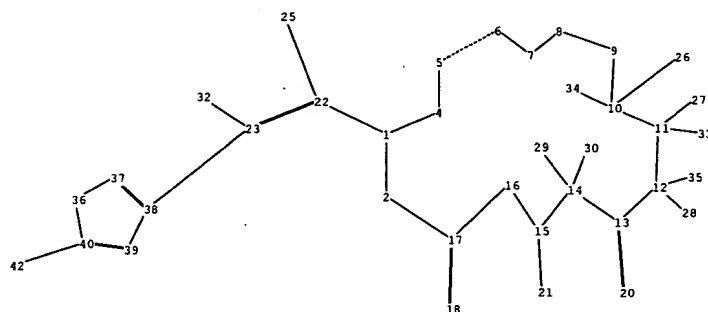
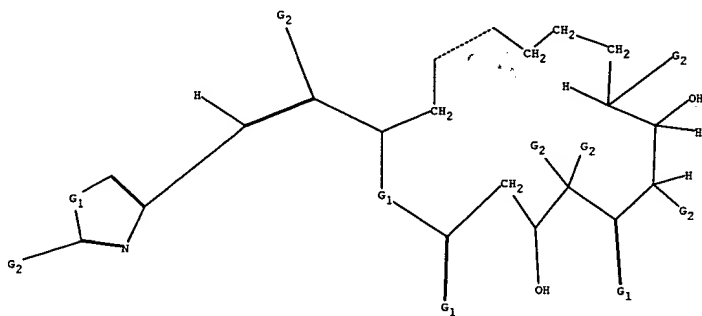


STN Structure : query.str



chain nodes :

18 20 21 22 23 25 26 27 28 29 30 32 33 34 35 42

ring nodes :

1 2 4 5 6 7 8 9 10 11 12 13 14 15 16 17 36 37 38 39 40

chain bonds :

1-22 10-26 10-34 11-27 11-33 12-28 12-35 13-20 14-30 14-29 15-21 17-18 22-23
22-25 23-32 23-38 40-42

ring bonds :

1-2 1-4 2-17 4-5 5-6 6-7 7-8 8-9 9-10 10-11 11-12 12-13 13-14 14-15 15-16
16-17 36-37 36-40 37-38 38-39 39-40

exact/norm bonds :

1-2 1-4 1-22 2-17 4-5 5-6 6-7 7-8 8-9 9-10 10-11 10-26 10-34 11-12 11-27
11-33 12-13 12-28 12-35 13-14 13-20 14-15 14-30 14-29 15-16 15-21 16-17 17-18
22-23 22-25 23-32 23-38 36-37 36-40 37-38 38-39 39-40 40-42

isolated ring systems :

containing 1 : 36 :

G1:O,S

G2:CH3,Et

Match level :

1:Atom 2:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom 12:Atom
13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:Atom 20:Atom 21:CLASS 22:CLASS
23:CLASS 25:CLASS 26:CLASS 27:CLASS 28:CLASS 29:CLASS 30:CLASS 32:CLASS 33:CLASS
34:CLASS 35:CLASS 36:Atom 37:Atom 38:Atom 39:Atom 40:Atom 42:CLASS

* * * * * Welcome to STN International * * * * *

NEWS 1 Web Page URLs for STN Seminar Schedule - N. America
NEWS 2 Apr 08 "Ask CAS" for self-help around the clock
NEWS 3 Apr 09 BEILSTEIN: Reload and Implementation of a New Subject Area
NEWS 4 Apr 09 ZDB will be removed from STN
NEWS 5 Apr 19 US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
NEWS 6 Apr 22 Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
NEWS 7 Apr 22 BIOSIS Gene Names now available in TOXCENTER
NEWS 8 Apr 22 Federal Research in Progress (FEDRIP) now available
NEWS 9 Jun 03 New e-mail delivery for search results now available
NEWS 10 Jun 10 MEDLINE Reload
NEWS 11 Jun 10 PCTFULL has been reloaded
NEWS 12 Jul 02 FOREGE no longer contains STANDARDS file segment
NEWS 13 Jul 22 USAN to be reloaded July 28, 2002;
 saved answer sets no longer valid
NEWS 14 Jul 29 Enhanced polymer searching in REGISTRY
NEWS 15 Jul 30 NETFIRST to be removed from STN
NEWS 16 Aug 08 CANCERLIT reload
NEWS 17 Aug 08 PHARMAMarketLetter(PHARMAML) - new on STN
NEWS 18 Aug 08 NTIS has been reloaded and enhanced
NEWS 19 Aug 09 JAPIO to be reloaded August 25, 2002
NEWS 20 Aug 19 Aquatic Toxicity Information Retrieval (AQUIRE).
 now available on STN
NEWS 21 Aug 19 IFIPAT, IFICDB, and IFIUDB have been reloaded
NEWS 22 Aug 19 The MEDLINE file segment of TOXCENTER has been reloaded

NEWS EXPRESS February 1 CURRENT WINDOWS VERSION IS V6.0d,
 CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP),
 AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002

NEWS HOURS STN Operating Hours Plus Help Desk Availability
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NEWS PHONE Direct Dial and Telecommunication Network Access to STN
NEWS WWW CAS World Wide Web Site (general information)

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FILE 'HOME' ENTERED AT 16:57:10 ON 22 AUG 2002

=> file reg

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

0.21

0.21

FILE 'REGISTRY' ENTERED AT 16:57:18 ON 22 AUG 2002

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DICTIONARY FILE UPDATES: 21 AUG 2002 HIGHEST RN 444646-89-3

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Calculated physical property data is now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

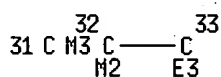
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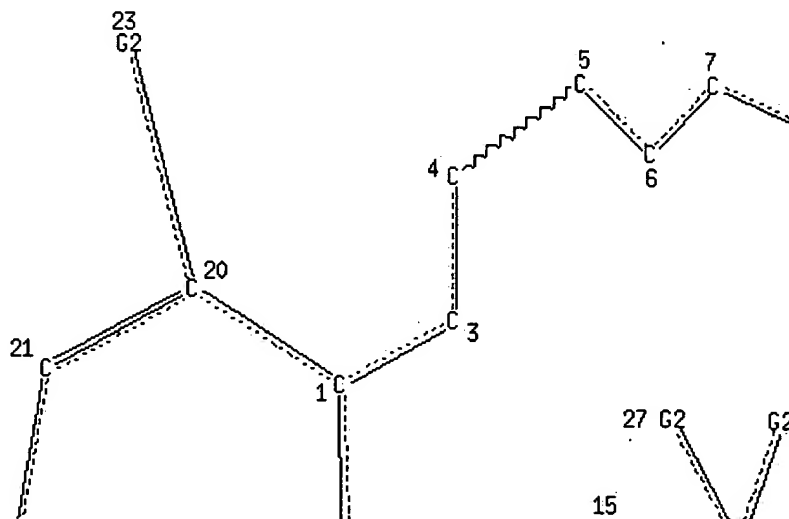
=> d 11

L1 HAS NO ANSWERS

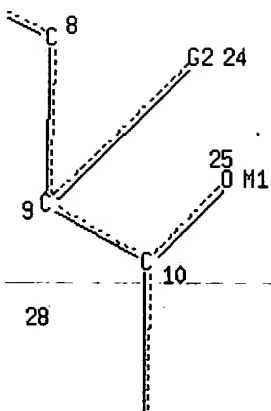
L1 STR



0 29 S 30

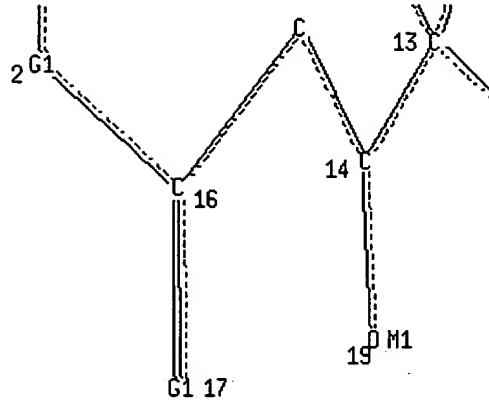


Page 1-A

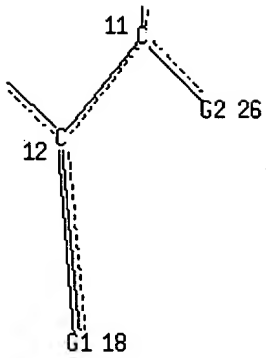


Page 1-B

Hu
22



Page 2-A



Page 2-B

VAR G1=29/30

VAR G2=31/32

NODE ATTRIBUTES:

HCOUNT	IS	M1	AT	19
HCOUNT	IS	M1	AT	25
HCOUNT	IS	M3	AT	31
HCOUNT	IS	M2	AT	32
HCOUNT	IS	E3	AT	33
NSPEC	IS	R	AT	1
NSPEC	IS	R	AT	2
NSPEC	IS	R	AT	3
NSPEC	IS	R	AT	4
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NSPEC	IS	R	AT	15
NSPEC	IS	R	AT	16
NSPEC	IS	C	AT	17
NSPEC	IS	C	AT	18
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NSPEC	IS	C	AT	25

NSPEC IS C AT 26
 NSPEC IS C AT 27
 NSPEC IS C AT 28
 DEFAULT MLEVEL IS ATOM
 MLEVEL IS CLASS AT 19 20 21 25 31 32 33
 DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
 RSPEC I
 NUMBER OF NODES IS 33

STEREO ATTRIBUTES: NONE

=> s 11

SAMPLE SEARCH INITIATED 17:02:40 FILE 'REGISTRY'
 SAMPLE SCREEN SEARCH COMPLETED - 1318 TO ITERATE

75.9% PROCESSED 1000 ITERATIONS 11 ANSWERS
 INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
 SEARCH TIME: 00.00.02

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
 BATCH **COMPLETE**
 PROJECTED ITERATIONS: 24183 TO 28537
 PROJECTED ANSWERS: 61 TO 517

L2 11 SEA SSS SAM L1

=> s 11 full

THE ESTIMATED SEARCH COST FOR FILE 'REGISTRY' IS 139.90 U.S. DOLLARS
 DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
 FULL SEARCH INITIATED 17:02:49 FILE 'REGISTRY'
 FULL SCREEN SEARCH COMPLETED - 25969 TO ITERATE

100.0% PROCESSED 25969 ITERATIONS 235 ANSWERS
 SEARCH TIME: 00.00.06

L3 235 SEA SSS FUL L1

=> file hcaplus

COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	143.32	143.53

FILE 'HCAPLUS' ENTERED AT 17:02:57 ON 22 AUG 2002
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 FILE LAST UPDATED: 21 Aug 2002 (20020821/ED)

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=> s 13

L4 134 L3

=> file reg

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

2.14

145.67

FILE 'REGISTRY' ENTERED AT 17:03:04 ON 22 AUG 2002

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STRUCTURE FILE UPDATES: 21 AUG 2002 HIGHEST RN 444646-89-3

DICTIONARY FILE UPDATES: 21 AUG 2002 HIGHEST RN 444646-89-3

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Calculated physical property data is now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:

<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

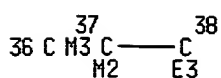
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L5 STRUCTURE UPLOADED

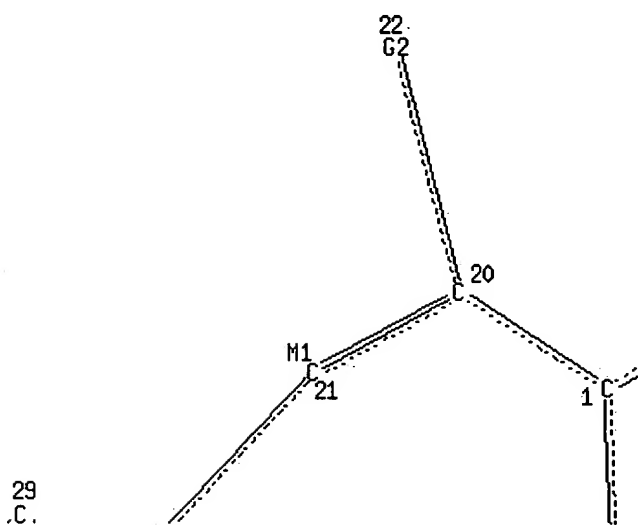
=> d 15

L5 HAS NO ANSWERS

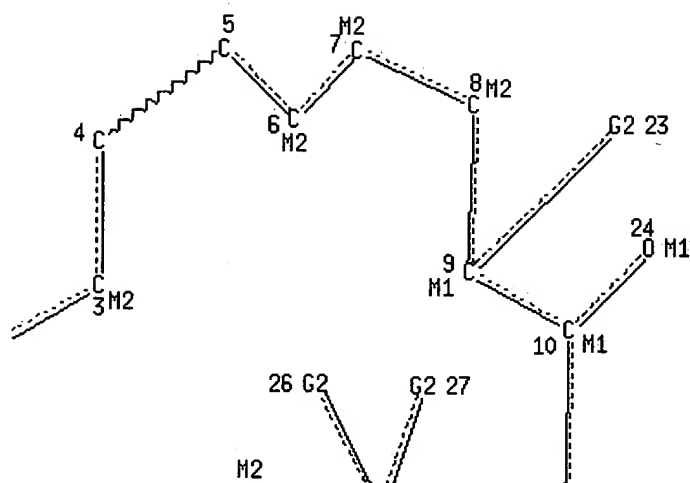
L5 STR



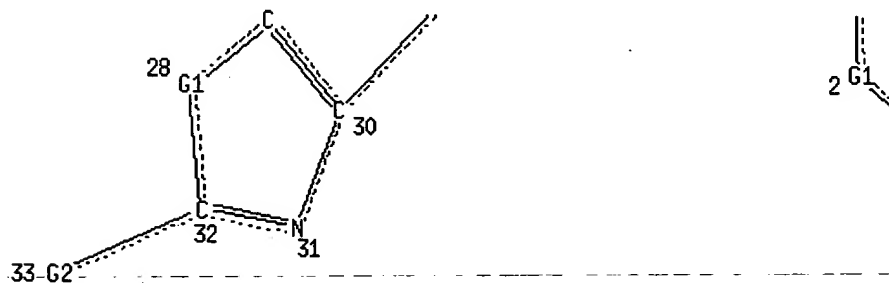
0 34 S 35



Page 1-A



Page 1-B



Page 2-A

NODE ATTRIBUTES:

8/22/02 5:11 PM

NSPEC IS R AT 32
 NSPEC IS C AT 33
 DEFAULT MLEVEL IS ATOM
 MLEVEL IS CLASS AT 19 20 21 24 36 37 38
 DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RSPEC I
 NUMBER OF NODES IS 38

STEREO ATTRIBUTES: NONE

=> s 15

SAMPLE SEARCH INITIATED 17:07:01 FILE 'REGISTRY'
 SAMPLE SCREEN SEARCH COMPLETED - 59 TO ITERATE

100.0% PROCESSED 59 ITERATIONS 8 ANSWERS
 SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
 BATCH **COMPLETE**
 PROJECTED ITERATIONS: 720 TO 1640
 PROJECTED ANSWERS: 8 TO 329

L6 8 SEA SSS SAM L5

=> s 15 full

THE ESTIMATED SEARCH COST FOR FILE 'REGISTRY' IS 139.90 U.S. DOLLARS
 DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
 FULL SEARCH INITIATED 17:07:08 FILE 'REGISTRY'
 FULL SCREEN SEARCH COMPLETED - 1042 TO ITERATE

100.0% PROCESSED 1042 ITERATIONS 121 ANSWERS
 SEARCH TIME: 00.00.03

L7 121 SEA SSS FUL L5

=> file hcaplus

COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	142.56	288.23

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=> s 17

L8 132 L7

=> s 18 and pd < september 1998

18872712 PD < SEPTEMBER 1998
(PD<19980900)

L9 34 L8 AND PD < SEPTEMBER 1998

=> s 18 and klar, u?/au

64 KLAR, U?/AU

L10 6 L8 AND KLAR, U?/AU

=> s 19 and klar, u?/au

64 KLAR, U?/AU

L11 0 L9 AND KLAR, U?/AU

=> d 110, ibib abs fhitr, 1-6

L10 ANSWER 1 OF 6 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
--------------	----------------------

ACCESSION NUMBER: 2002:132142 HCAPLUS

DOCUMENT NUMBER: 136:309773

TITLE: Synthesis and biological activity of epothilones

AUTHOR(S): Klar, Ulrich; Skuballa, Werner; Buchmann, Bernd;
Schwede, Wolfgang; Bunte, Thomas; Hoffmann, Jens;
Lichtner, Rosemarie B.

CORPORATE SOURCE: Research Laboratories of Schering AG, Berlin, D-13342,
Germany

SOURCE: ACS Symposium Series (2001), 796(Anticancer Agents),
131-147

CODEN: ACSMC8; ISSN: 0097-6156

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. The total synthesis and biol. activity of epothilone analogs are described. Selected SAR data indicate the possibility to improve activity and selectivity by structural modifications. The new compds. may help to elucidate the therapeutic potential of this class of anticancer drugs.

IT 189453-10-9D, Epothilone D, analogs

RL: MSC (Miscellaneous)

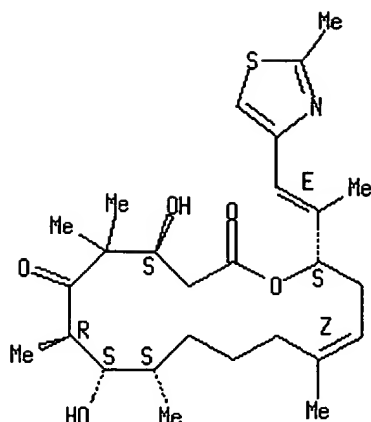
(review of the synthesis and biol. activity of epothilones)

RN 189453-10-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-
[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-
(9CI) (CA INDEX NAME)

.. Absolute stereochemistry.. Rotation (-)...

Double bond geometry as shown.



REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 2 OF 6 HCAPLUS COPYRIGHT 2002 ACS

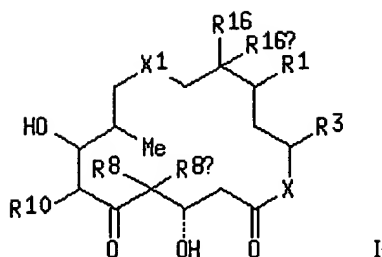
Full Text	Citing References
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ACCESSION NUMBER: 2001:780370 HCAPLUS
DOCUMENT NUMBER: 135:331294
TITLE: Preparation of epothilone derivatives for pharmaceutical use in the treatment of cancer
INVENTOR(S): Buchmann, Bernd; Klar, Ulrich; Skuballa, Werner; Schwede, Wolfgang; Hoffmann, Jens; Lichtner, Rosemarie
PATENT ASSIGNEE(S): Schering A.-G., Germany
SOURCE: Ger. Offen., 42 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

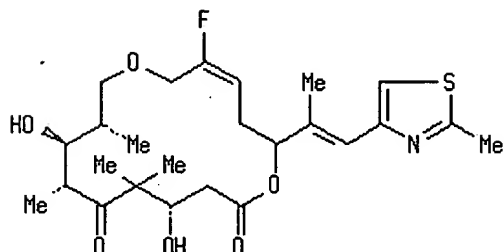
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10020517	A1	20011025	DE 2000-10020517	20000419
WO 2001081342	A2	20011101	WO 2001-EP4552	20010419
WO 2001081342	A3	20020510		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: DE 2000-10020517 A 20000419
OTHER SOURCE(S): MARPAT 135:331294
GI



I



II

AB Epothilones, such as I [R3 = heteroaryl, heteroarylalkenyl, heteroarylhaloalkenyl, etc.; R8, R8a = H, alkyl, arylalkyl; R8R8a = alkylene, heteroalkene; R10 = H, alkyl, alkenyl, alkynyl; R1R16a = bond, O; R16 = H, CN, alkyl, halogen; X = O, NH; X1 = O, CH2], were prepd. for a variety of therapeutic uses, such as treatment of malignant tumors, proliferative diseases, leukemia, and chronic inflammatory diseases. Thus, epothilone II was prepd. via a multistep synthetic sequence starting from (3S)-dihydro-3-hydroxy-4,4-dimethyl-2(3H)-furanone, L-(-)-malic acid, and [(2-methyl-4-thiazolyl)methyl]phosphonic acid di-Et ester. Pharmaceutical formulations of the prepd. oxa-epothilones were discussed, but specific biol. activity data was not presented.

IT 369646-16-2P

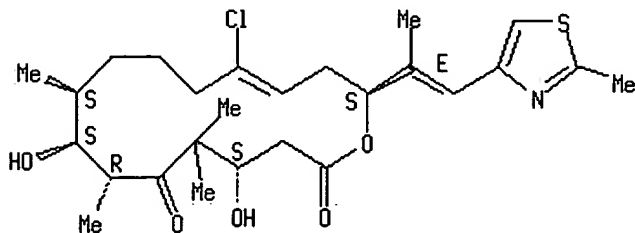
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of epothilone derivs. for pharmaceutical use in the treatment of cancer)

RN 369646-16-2 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 13-chloro-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,16S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry as described by E or Z.



L10 ANSWER 3 OF 6 HCAPLUS COPYRIGHT 2002 ACS

Full Text Citing References

ACCESSION NUMBER: 2001:729040 HCAPLUS
DOCUMENT NUMBER: 136:95676
TITLE: Subcellular distribution of epothilones in human tumor cells
AUTHOR(S): Lichtner, R. B.; Rotgeri, A.; Bunte, T.; Buchmann, B.; Hoffmann, J.; Schwede, W.; Skuballa, W.; Klar, U.

CORPORATE SOURCE: Research Laboratories of Schering AG, Berlin, 13342, Germany
 SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2001), 98(20), 11743-11748
 CODEN: PNASA6; ISSN: 0027-8424
 PUBLISHER: National Academy of Sciences
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB Epothilones are a new class of natural and potent antineoplastic agents that stabilize microtubules. Although 12,13-epoxide derivs. are potent antiproliferative agents, the activities of the corresponding 12,13-olefin analogs are significantly decreased. These data were confirmed for two new analogs, 6-propyl-EpoB (pEB) and 6-propyl-EpoD (pED); in comparison with the natural compds. EpoB/EpoD, by using human A431, MCF7, and MDR1-overexpressing NCI/Adr cells. By using tritiated pEB/pED, compd. uptake, release, and nuclear accumulation were investigated in A431 and NCI/Adr cells. In these cells, epothilones can principally be recognized and exported by verapamil-sensitive efflux pumps, which are not identical to MDR1. The degree of export depends on the structure, olefin vs. epoxide-analog, and also on the intracellular drug concn. The accumulation of pED used at 3.5 or 70 nM, resp., was increased in the presence of 10 µM Verapamil in both cell lines 2- to 8-fold. In contrast, the intracellular levels of pEB were affected by Verapamil only at 3.5 nM pEB in NCI/Adr (2-fold) and not in A431 cells. In addn., strong nuclear accumulation was obsd. for pEB (40-50%) but not paclitaxel or pED (5-15%) in both cell lines. Our study suggests that differences in growth inhibitory efficacy between epoxide and olefin analogs may be based on different mechanisms of drug accumulation and subcellular distribution.

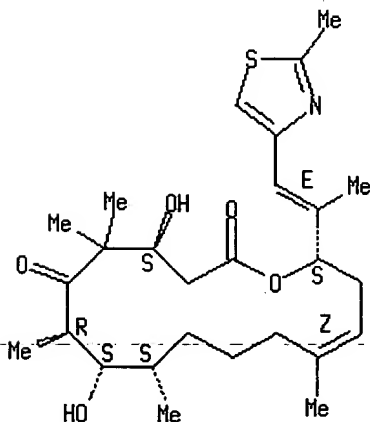
IT 189453-10-9, Epothilone D

RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (subcellular distribution of antitumor epothilones in human tumor cells)

RN 189453-10-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
 Double bond geometry as shown.



REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

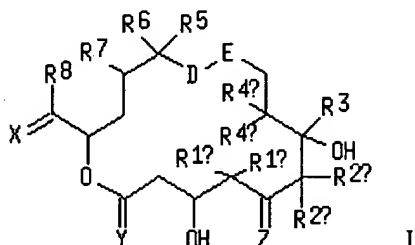
L10 ANSWER 4 OF 6 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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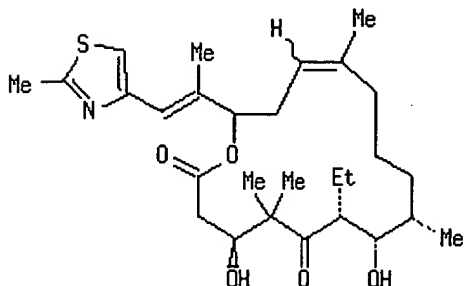
ACCESSION NUMBER: 2000:738730 HCAPLUS
 DOCUMENT NUMBER: 133:309795
 TITLE: Preparation of new epothilone derivatives and their pharmaceutical uses
 INVENTOR(S): Klar, Ulrich; Schwede, Wolfgang; Skuballa, Werner; Buchmann, Bernd; Schirner, Michael
 PATENT ASSIGNEE(S): Schering A.-G., Germany
 SOURCE: Ger. Offen., 74 pp.
 CODEN: GWXXBX
 DOCUMENT TYPE: Patent
 LANGUAGE: German
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19908767	A1	20001019	DE 1999-19908767	19990218

OTHER SOURCE(S): MARPAT 133:309795
 GI



I



II

AB New epothilone derivs. I (R1a,R1b = R2a,R2b = same or different H, alkyl, aryl, aralkyl or (CH2)m,n m, n = 2-5; R3 = H, alkyl, aryl, aralkyl; R4a,R4b = same or different H, alkyl, aryl, aralkyl or (CH2)p = 2-5, CH2CH2, CH=CH, C≡C, epoxy, CH(OH)CH(OH), CH(OH)CH2; D-E = a group; R5 = H, alkyl, aryl, aralkyl; R6,R7 = H, bond, O; R8 = H, alkyl, aryl, aralkyl; X = O, OR23 alkylene-α,-ω-dioxy group straight or branched, OR9 or the CR10R11 group where R23 = alkyl, R9 = H or protecting group and R10,R11 = same or different H, alkyl, aryl, aralkyl or R10,R11 = together with methylene are a 5-7 membered carbocyclic ring; Y = O or two H; Z = O or H/OR12 and R12 = H or a protecting group) were prepd. Thus E- and Z-II were prepd. via a multistep synthesis. I cooperate with tubulin by stabilizing formed microtubuli. I are able phasespecifically to affect the cell division and are suitable for the treatment of malignant ovarian, stomach, colon, adeno, breast, lung, head and neck tumors, malignant melanomas, acute lymphocytic and myelocytic leukemia. Derivs. of I are suitable for use in anti-angiogenic therapy as well as for treating chronic inflammatory diseases (psoriasis, arthritis). In order to prevent uncontrolled cell proliferations and to improve the compatibility of medical implants I can be applied or incorporated into polymeric

materials. I can be used alone or to achieve additive or synergistic effects in combination with further principles and substance classes applicable in tumor therapy.

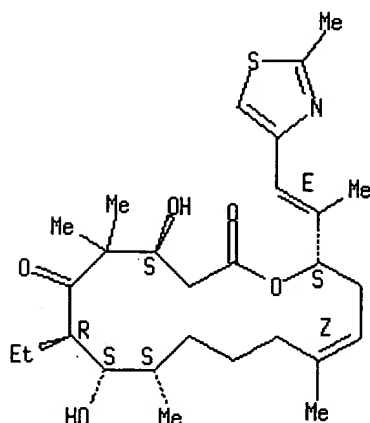
IT 220773-43-3P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of new epothilone derivs. and their pharmaceutical uses)

RN 220773-43-3 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 7-ethyl-4,8-dihydroxy-5,5,9,13-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L10 ANSWER 5 OF 6 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER: 2000:15195 HCAPLUS
DOCUMENT NUMBER: 132:64110
TITLE: The preparation process, intermediate products and pharmaceutical use of epothilone derivatives
INVENTOR(S): Buchmann, Bernd; Klar, Ulrich; Skuballa, Werner; Schwede, Wolfgang; Schirner, Michael; Menrad, Andreas
PATENT ASSIGNEE(S): Schering A.-G., Germany
SOURCE: PCT Int. Appl., 86 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 200000485	A1	20000106	WO 1999-EP4915	19990630
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
DE 19830060	A1	20000210	DE 1998-19830060	19980630
DE 19923001	A1	20001116	DE 1999-19923001	19990513
AU 9950369	A1	20000117	AU 1999-50369	19990630

PRIORITY APPLN. INFO.:

DE 1998-19830060 A 19980630
DE 1999-19923001 A 19990513
WO 1999-EP4915 W 19990630

OTHER SOURCE(S): CASREACT 132:64110; MARPAT 132:64110
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention relates to new epothilone derivs. I [R1a, R1b = H, C1-10-alkyl, aryl, C7-10-aralkyl; R1aR1b = (CH2)m, m = 2 - 5; R2a, R2b = H, C1-10-alkyl, aryl, C7-10-aralkyl; R2aR2b = (CH2)n, n = 2 - 5; R3 = H, C1-10-alkyl, aryl, C7-10-aralkyl; R4a, R4b = H, C1-10-alkyl, aryl, C7-10-aralkyl; R4aR4b = (CH2)m, m = 2 - 5; D-E = CH2CH2, CH:CH, C≡C, oxirane ring, CH(OH)CH(OH), CH(OH)CH2; R5 = C1-10-alkyl, aryl, C7-10-aralkyl; R6, R7 = H; R6R7 = O, bond; R8 = C1-10-alkyl, aryl, C7-10-aralkyl; R25 = H, C1-10-alkyl, C1-10-hydroxyalkyl, C1-10-haloalkyl; X = O, (OR9)2, C2-10-alkylene-α,ω-dioxy, CR11R12; CX = CH(OR10); R9 = C1-20-alkyl; R10 = H, protecting group; R11, R12 = H, C1-10-alkyl, aryl, C7-10-aralkyl; R11R12 = CH2, C5-7-carbocyclic ring; Y = O, CY = CH2; CZ = CH(OR13), R13 = H, protecting group] which are prepd. via cyclization of ketones II [R15 = H, OH halogen, OR15a, OSO2R15b; R15a = H, SO2-alkyl, SO2-aryl, SO2-aralkyl, (CH2)o, CR16aR16b; R15b = H, C1-20-alkyl, aryl, C7-20-aralkyl; R16a, R16b = H, C1-10-alkyl, aryl, C7-20-aralkyl; R16aR16b = (CH2)q; o = 2 - 4; q = 3 - 6]. Thus, epothilone deriv. III was prepd. via macrolactonization of carboxylic acid IV with 2,4,6-trichlorobenzoyl chloride and Et3N in THF followed by deprotection with aq. CF3CO2H in CH2Cl2. I cooperate with tubulin by stabilizing formed microtubuli.

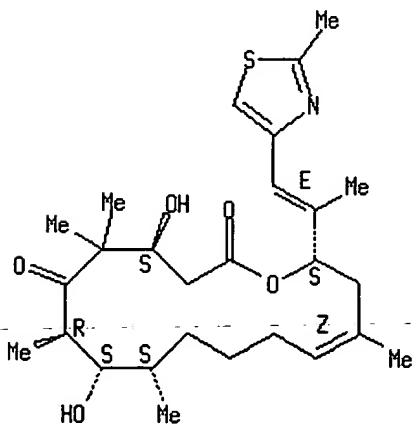
IT 253447-39-1P

RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and pharmaceutical use of epothilone derivs.)

RN 253447-39-1 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9,14-pentamethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



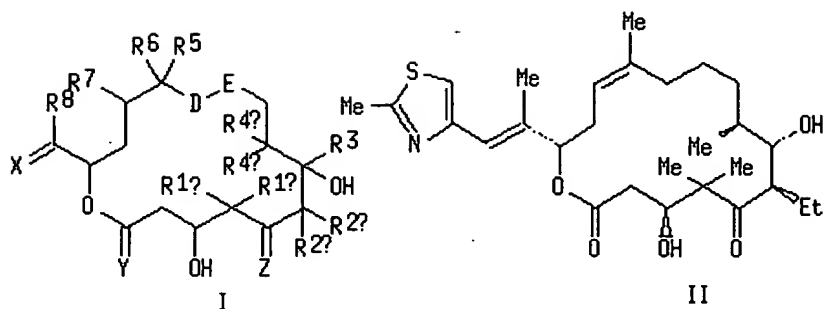
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER: 1999:126888 HCAPLUS
 DOCUMENT NUMBER: 130:196529
 TITLE: Preparation of new epothilone derivatives as
 pharmaceutical agents
 INVENTOR(S): Klar, Ulrich; Schwede, Wolfgang; Skuballa, Werner;
 Buchmann, Bernd; Schirner, Michael
 PATENT ASSIGNEE(S): Schering Aktiengesellschaft, Germany
 SOURCE: PCT Int. Appl., 185 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: German
 FAMILY ACC. NUM. COUNT: 4
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9907692	A2	19990218	WO 1998-EP5064	19980810
WO 9907692	A3	19990514		
W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
DE 19735574	A1	19990211	DE 1997-19735574	19970809
DE 19735575	A1	19990211	DE 1997-19735575	19970809
DE 19735578	A1	19990211	DE 1997-19735578	19970809
DE 19748928	A1	19990429	DE 1997-19748928	19971024
DE 19749717	A1	19990506	DE 1997-19749717	19971031
DE 19751200	A1	19990520	DE 1997-19751200	19971113
DE 19813821	A1	19990923	DE 1998-19813821	19980320
AU 9893409	A1	19990301	AU 1998-93409	19980810
EP 1005465	A2	20000607	EP 1998-946309	19980810
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO			
JP 2001512723	T2	20010828	JP 2000-506196	19980810
ZA 9810403	A	20000515	ZA 1998-10403	19981113
PRIORITY APPLN. INFO.:			DE 1997-19735574 A	19970809
			DE 1997-19735575 A	19970809
			DE 1997-19735578 A	19970809
			DE 1997-19748928 A	19971024
			DE 1997-19749717 A	19971031
			DE 1997-19751200 A	19971113
			DE 1998-19813821 A	19980320
			WO 1998-EP5064 W	19980810
OTHER SOURCE(S):	MARPAT 130:196529			
GI				



AB Epothilone derivs. of formula I [X = O, alkylene- α,ω -dioxy, two alkoxy groups, etc.; Y = O, H₂; Z = O, (H, OH), (H, protected OH); R_{1a}, R_{1b} = H, alkyl, aryl, aralkyl, or together = (CH₂)_m where m = 2, 3, 4, 5; R_{2a}, R_{2b} = H, alkyl, aryl, aralkyl, or together = (CH₂)_n where n = 2, 3, 4, 5; when D-E = CH₂CH₂ or when Y = O, R_{2a} or R_{2b} may not be H/Me; R₃ = H, alkyl, aryl, aralkyl; R_{4a}, R_{4b} = H, alkyl, aryl, aralkyl, or together = (CH₂)_p where p = 2, 3, 4, 5; D-E = CH₂CH₂, CH:CH, C \equiv C, 2,3-oxiranediy, CH(OH)CH(OH), CH(OH)CH₂; R₅ = H, alkyl, aryl, aralkyl; R₆, R₇ = H, together = a satd. bond or O; R₈ = H, alkyl, aryl, aralkyl all of which may be substituted] are prepd. Thus, the title compds. (4S,7R,8S,9S,13E,16S(E))- and (4S,7R,8S,9S,13Z,16S(E))-4,8-dihydroxy-7-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethylcyclohexadec-13-en-2,6-dione (II) were prepd. in many steps. The new compds. interact with tubulin by stabilizing formed microtubuli. They are capable of influencing cell division in a phase-specific manner and are suitable for the treatment of malignant tumors, such as ovarian, gastric, colon, breast, lung, head and neck carcinoma, adenocarcinoma, malignant melanoma, and acute lymphocytic and myelocytic leukemia. They are also suited for anti-angiogenesis therapy and for the treatment of chronic inflammatory diseases (psoriasis, arthritis). To prevent uncontrolled cell growth on, and for better tolerability of, medical implants, the derivs. can be introduced into or applied to polymeric materials. The compds. provided for in the invention can be used alone or, to achieve additive or synergistic effects, in combination with other principles and substance categories used in tumor therapy.

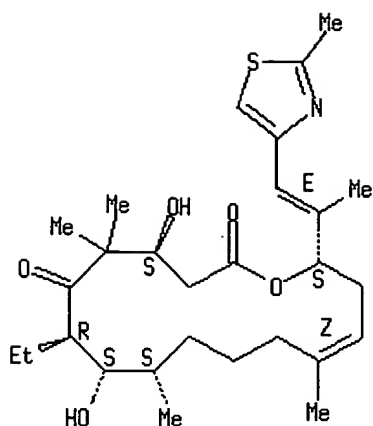
IT 220773-43-3P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of epothilone derivs. as antitumor agents)

RN 220773-43-3 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 7-ethyl-4,8-dihydroxy-5,5,9,13-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



=> d his

(FILE 'HOME' ENTERED AT 16:57:10 ON 22 AUG 2002)

FILE 'REGISTRY' ENTERED AT 16:57:18 ON 22 AUG 2002

L1 STRUCTURE UPLOADED

L2 11 S L1

L3 235 S L1 FULL

FILE 'HCAPLUS' ENTERED AT 17:02:57 ON 22 AUG 2002

L4 134 S L3

FILE 'REGISTRY' ENTERED AT 17:03:04 ON 22 AUG 2002

L5 STRUCTURE UPLOADED

L6 8 S L5

L7 121 S L5 FULL

FILE 'HCAPLUS' ENTERED AT 17:07:15 ON 22 AUG 2002

L8 132 S L7

L9 34 S L8 AND PD < SEPTEMBER 1998

L10 6 S L8 AND KLAR, U?/AU

L11 0 S L9 AND KLAR, U?/AU

=> s 19 not 110

L12 34 L9 NOT L10

=> d 112, ibib abs fhittstr, 1-34

L12 ANSWER 1 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER: 2000:316343 HCAPLUS
Correction of: 1997:528752

DOCUMENT NUMBER: 132:293587
Correction of: 127:149021

TITLE: The Olefin Metathesis Approach to Epothilone A and Its Analogs

AUTHOR(S): Nicolaou, K. C.; He, Y.; Vourloumis, D.; Vallberg, H.;
Roschangar, F.; Sarabia, F.; Ninkovic, S.; Yang, Z.;
Trujillo, J. I.

CORPORATE SOURCE: Institute for Chemical Biology, La Jolla, CA, 92037,
USA

SOURCE: Journal of the American Chemical Society (1997),
119(34), 7960-7973

CODEN: JACSAT; ISSN: 0002-7863

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE:
GI

English

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The olefin metathesis approach to epothilone A (I) and several diastereomeric analogs is described. Key building blocks II, (S)-OHCH(Me)CH₂CH₂CH=CH₂, and (S)-MeCH₂COC(Me)₂CH(OSiMe₂CMe₃)CH₂CO₂H were constructed in optically active form and were coupled and elaborated to olefin metathesis precursor III (R = SiMe₂CMe₃) via an aldol reaction and an esterification coupling. Olefin metathesis of compd. III (R = SiMe₂CMe₃), under the catalytic influence of RuCl₂(:CHPh)(PCy₃)₂, furnished cis- and trans-cyclic olefins IV (R = SiMe₂CMe₃). Epoxidn. of (Z)-IV (R = H) gave I and several analogs, whereas epoxidn. of (E)-IV (R = H) resulted in addnl. epothilones. Similar elaboration of isomeric as well as simpler intermediates resulted in yet another series of epothilone analogs and model systems.

IT 186692-73-9P

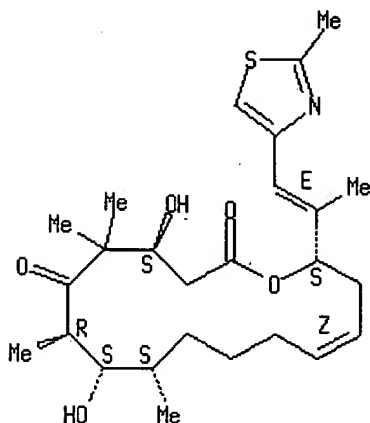
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(synthesis of epothilone A and analogs via olefin metathesis)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L12 ANSWER 2 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER: 1999:19340 HCAPLUS

DOCUMENT NUMBER: 130:217758

TITLE: Desoxyepothilone-B is curative against human tumor xenografts that are refractory to paclitaxel

AUTHOR(S): Chou, Ting-Chao; Zhang, Xiu-Guo; Harris, Christina R.; Kuduk, Scott D.; Balog, Aaron; Savin, Kenneth A.; Bertino, Joseph R.; Danishefsky, Samuel J.

CORPORATE SOURCE: Molecular Pharmacology and Therapeutics Program, Sloan-Kettering Institute for Cancer Research, New York, NY, 10021, USA

SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1998), 95(26), 15798-15802
CODEN: PNASA6; ISSN: 0027-8424

PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The epothilones are naturally occurring, cytotoxic macrolides that function through a paclitaxel (Taxol)-like mechanism. Although structurally dissimilar, both classes of mols. lead to the arrest of cell division and eventual cell death by stabilizing cellular microtubule assemblies. The epothilones differ in their ability to retain activity against multidrug-resistant (MDR) cell lines and tumors where paclitaxel fails. In the current account, we focus on the relationship between epothilone and paclitaxel in the context of tumors with multiple drug resistance. The epothilone analog Z-12,13-desoxyepothilone B (dEpoB) is >35,000-fold more potent than paclitaxel in inhibiting cell growth in the MDR DC-3F/ADX cell line. Various formulations, routes, and schedules of i.v. administration of dEpoB have been tested in nude mice. Slow infusion with a Cremophor-ethanol vehicle proved to be the most beneficial in increasing efficacy and decreasing toxicity. Although dEpoB performed similarly to paclitaxel in sensitive tumors xenografts (MX-1 human mammary and HT-29 colon tumor), its effects were clearly superior against MDR tumors. When dEpoB was administered to nude mice bearing our MDR human lymphoblastic T cell leukemia (CCRF-CEM/paclitaxel), dEpoB demonstrated a full curative effect. For human mammary adenocarcinoma MCF-7/Adr cells refractory to paclitaxel, dEpoB reduced the established tumors, markedly suppressed tumor growth, and surpassed other commonly used chemotherapy drugs such as adriamycin, vinblastine, and etoposide in beneficial effects.

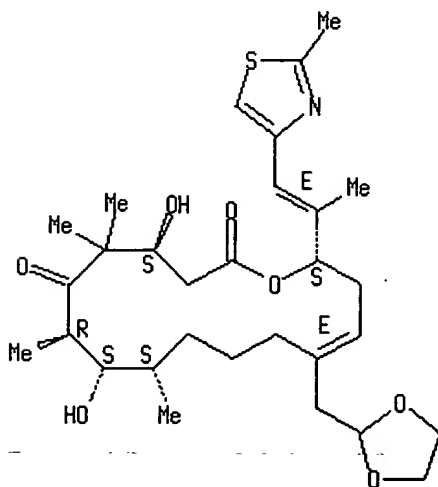
IT 198475-07-9

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study) (antitumor activity of desoxyepothilone B analogs)

RN 198475-07-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 13-(1,3-dioxolan-2-ylmethyl)-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13E,16S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



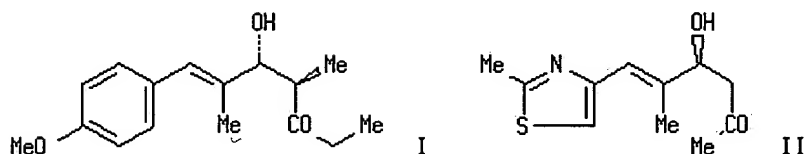
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 3 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text Citing References

ACCESSION NUMBER: 1998:805542 HCAPLUS
DOCUMENT NUMBER: 130:153488

TITLE: The antibody catalysis route to the total synthesis of epothilones
 AUTHOR(S): Sinha, Subhash C.; Barbas, Carlos F., III; Lerner, Richard A.
 CORPORATE SOURCE: The Skaggs Institute for Chemical Biology and the Department of Molecular Biology, The Scripps Research Institute, La Jolla, CA, 92037, USA
 SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1998), 95(25), 14603-14608
 CODEN: PNASA6; ISSN: 0027-8424
 PUBLISHER: National Academy of Sciences
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 OTHER SOURCE(S): CASREACT 130:153488
 GI



AB A total synthesis of epothilones A and C via antibody-catalyzed aldol and retro-aldol reactions was described. Epothilone precursors (+)-I and (-)-II were prep'd. using aldolase antibody 38C2 as a catalyst. These precursors were then converted to epothilones A and C to complete the total synthesis.

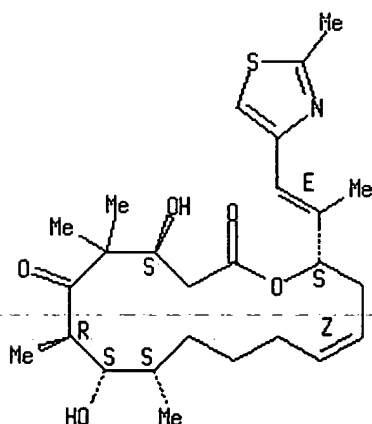
IT **186692-73-9P**, Epothilone C

RL: BPN (Biosynthetic preparation); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
 (total synthesis of epothilones via antibody 38C2 catalyzed retro-aldol reactions)

RN **186692-73-9** HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
 Double bond geometry as shown.



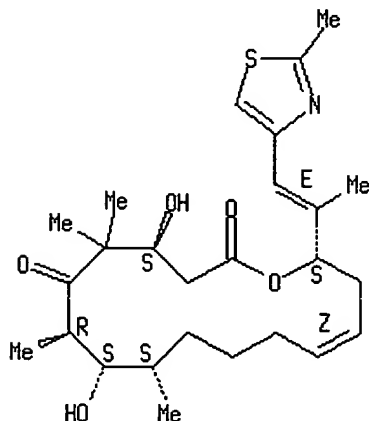
REFERENCE COUNT: 62 THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 4 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text Citing References

ACCESSION NUMBER: 1998:760826 HCAPLUS
 DOCUMENT NUMBER: 130:95407
 TITLE: Derivatization of the C12-C13 functional groups of
 epothilones A, B and C
 AUTHOR(S): Sefkow, Michael; Kiffe, Michael; Hofle, Gerhard
 CORPORATE SOURCE: Gesellschaft fur Biotechnologische Forschung mbH, Abt.
 Naturstoffchemie, Braunschweig, D-38124, Germany
 SOURCE: Bioorganic & Medicinal Chemistry Letters (1998),
 8(21), 3031-3036
 CODEN: BMCLE8; ISSN: 0960-894X
 PUBLISHER: Elsevier Science Ltd.
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 OTHER SOURCE(S): CASREACT 130:95407
 AB Epothilone A reacted with hydrohalic acids to give C12-C13 halohydrin
 regioisomers (ratios: 2:1 - 4:1), whereas epothilone B gave under the same
 conditions the isomerically pure C12 halo C13 hydroxy deriv. With
 non-nucleophilic Bronstedt acids and with Lewis acids a highly solvent
 dependent product distribution and some unexpected rearrangement products
 were obsd. Epothilone C bearing a double bond between C12 and C13 was
 regioselectively dihydroxylated or hydrogenated at that position.
 IT **186692-73-9**, Epothilone C
 RL: RCT (Reactant); RACT (Reactant or reagent)
 (derivatization of the C12-C13 functional groups of epothilones A, B
 and C)
 RN **186692-73-9** HCAPLUS
 CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-
 [(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-
 (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
 Double bond geometry as shown.



REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

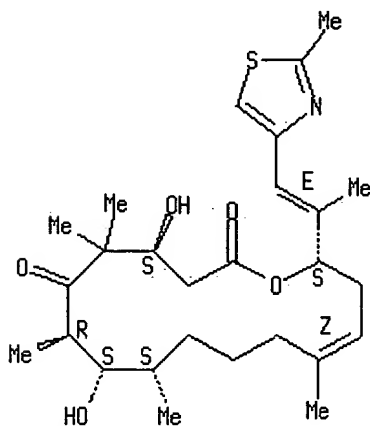
L12 ANSWER 5 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER:	1998:732784 HCAPLUS
DOCUMENT NUMBER:	130:81320
TITLE:	Easy access to the epothilone family - synthesis of epothilone B
AUTHOR(S):	Mulzer, Johann; Mantoulidis, Andreas; Ohler, Elisabeth
CORPORATE SOURCE:	Inst. fur Organische Chemie, Univ. Wien, Vienna, A-1090, Austria
SOURCE:	Tetrahedron Letters (1998), 39(47), 8633-8636 CODEN: TELEAY; ISSN: 0040-4039
PUBLISHER:	Elsevier Science Ltd.

DOCUMENT TYPE: Journal
 LANGUAGE: English
 OTHER SOURCE(S): CASREACT 130:81320
 AB An easy access to four out of five naturally occurring epothilones (A-E) is reported. Key steps are an enantioselective Mukaiyama type aldol reaction, (E)- and (Z)-selective olefinations, and a sulfone alkylation.
 IT **189453-10-9P**, Epothilone D
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (synthesis of epothilone B)
 RN 189453-10-9 HCAPLUS
 CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
 Double bond geometry as shown.

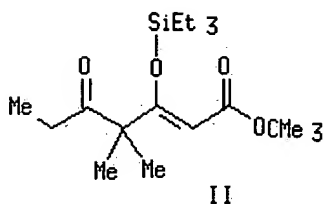
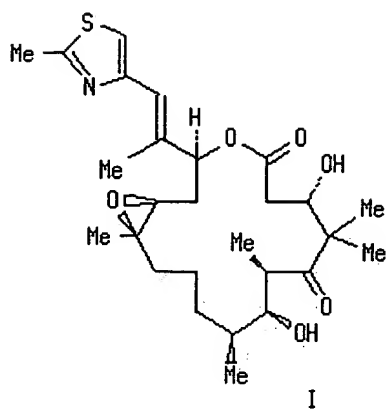


REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 6 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER: 1998:726876 HCAPLUS
 DOCUMENT NUMBER: 130:81319
 TITLE: A novel aldol condensation with 2-methyl-4-pentenal and its application to an improved total synthesis of epothilone B
 AUTHOR(S): Balog, Aaron; Harris, Christina; Savin, Kenneth; Zhang, Xiu-Guo; Chou, Ting Chao; Danishefsky, Samuel J.
 CORPORATE SOURCE: Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, New York, NY, 10021, USA
 SOURCE: Angewandte Chemie, International Edition (1998), 37(19), 2675-2678
 CODEN: ACIEF5; ISSN: 1433-7851
 PUBLISHER: Wiley-VCH Verlag GmbH
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 OTHER SOURCE(S): CASREACT 130:81319
 GI



AB Epothilone B was prepd. in 9 steps via aldol condensation of (S)-2-methyl-4-pentenal with the enolate I.

IT **189453-10-9P**

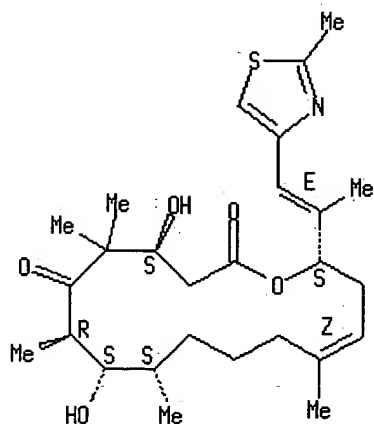
RL: SPN (Synthetic preparation); PREP (Preparation)

(novel aldol condensation with 2-methyl-4-pentenal and application to improved total synthesis of epothilone B)

RN 189453-10-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 7 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Citing
Text References

ACCESSION NUMBER: 1998:534644 HCAPLUS

DOCUMENT NUMBER: 129:239597

TITLE: Desoxyepothilone B: an efficacious microtubule-targeted antitumor agent with a promising in vivo profile relative to epothilone B
AUTHOR(S): Chou, Ting-Chao; Zhang, Xiu-Guo; Balog, Aaron; Su, Dai-Shi; Meng, Dongfang; Savin, Kenneth; Bertino, Joseph R.; Danishefsky, Samuel J.
CORPORATE SOURCE: Molecular Pharmacology and Therapeutics Program, Cornell University Graduate School of Medical Sciences, New York, NY, 10021, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1998), 95(16), 9642-9647

CODEN: PNASA6; ISSN: 0027-8424

PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A new class of 16-membered macrolides, the epothilones (Epos), has been synthesized and evaluated for antitumor potential in vitro and in vivo. Recent studies in these and other labs. showed that epothilones and paclitaxel (paclitaxel) share similar mechanisms of action in stabilizing microtubule arrays as indicated by binding-displacement studies, substitution for paclitaxel in paclitaxel-dependent cell growth, and electron microscopic examns. The present study examd. cell growth-inhibitory effects in two rodent and three human tumor cell lines and their drug-resistant sublines. Although paclitaxel showed as much as 1,970-fold cross-resistance to the sublines resistant to paclitaxel, adriamycin, vinblastine, or actinomycin D, most epothilones exhibit little or no cross-resistance. In multidrug-resistant CCRF-CEM/VBL100 cells, IC50 values for EpoA (1), EpoB (2), desoxyEpoA (3) (dEpoA), desoxyEpoB (4) (dEpoB), and paclitaxel were 0.02, 0.002, 0.012, 0.017, and 4.14 μ M, resp. In vivo studies, using i.p. administration, indicated that the parent, EpoB, was highly toxic to mice and showed little therapeutic effect when compared with a lead compd., dEpoB. More significantly, dEpoB (25-40 mg/kg, Q2Dx5, i.p.) showed far superior therapeutic effects and lower toxicity than paclitaxel, doxorubicin, camptothecin, or vinblastine (at maximal tolerated doses) in parallel expts. For mammary adenocarcinoma xenografts resistant to adriamycin, MCF-7/Adr, superior therapeutic effects were obtained with dEpoB compared with paclitaxel when i.p. regimens were used. For ovarian adenocarcinoma xenografts, SK-OV-3, dEpoB (i.p.), and paclitaxel (i.v.) gave similar therapeutic effects. In nude mice bearing a human mammary carcinoma xenograft (MX-1), marked tumor regression and cures were obtained with dEpoB.

IT **189453-10-9**, Desoxyepothilone B

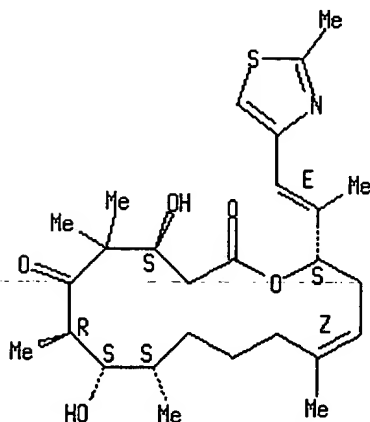
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(desoxyepothilone B is an efficacious microtubule-targeted antitumor agent with a promising in vivo profile relative to epothilone B)

RN **189453-10-9** HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L12 ANSWER 8 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER: 1998:503765 HCAPLUS
 DOCUMENT NUMBER: 129:244965
 TITLE: Synthesis and biological properties of
 C12,13-cyclopropyl-epothilone A and related
 epothilones
 AUTHOR(S): Nicolaou, K. C.; Finlay, M. Ray V.; Ninkovic, Sacha;
 King, N. Paul; He, Yun; Li, Tianhu; Sarabia,
 Francisco; Vourloumis, Dionisios
 CORPORATE SOURCE: Dep. Chemistry, The Skaggs Inst. Chem. Biol., The
 Scripps Res. Inst., La Jolla, CA, 92037, USA
 SOURCE: Chemistry & Biology (1998), 5(7), 365-372
 CODEN: CBOLE2; ISSN: 1074-5521
 PUBLISHER: Current Biology Ltd.
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 OTHER SOURCE(S): CASREACT 129:244965
 AB Background: The epothilones are natural substances that are potently
 cytotoxic, having an almost identical mode of action to Taxol as
 tubulin-polymn. and microtubule-stabilizing agents. The development of
 detailed structure-activity relationships for these compds. and the
 further elucidation of their mechanism of action is of high priority.
 Results: The chem. synthesis of the C12,13-cyclopropyl analog of
 epothilone A and its C12,13-trans-diastereoisomer has been accomplished.
 These compds. and several other epothilone analogs have been screened for
 their ability to induce tubulin polymn. and death of a no. of tumor cells.
 Several interesting structure-activity trends within this family of
 compds. were identified. Conclusions: The results of the biol. tests
 conducted in this study have demonstrated that, although a no. of
 positions on the epothilone skeleton are amenable to modification without
 significant loss of biol. activity, the replacement of the epoxide moiety
 of epothilone A with a cyclopropyl group leads to total loss of activity.

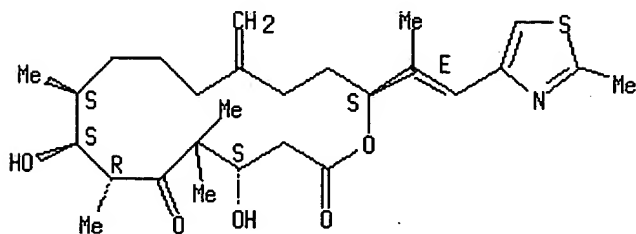
IT **213312-66-4**

RL: RCT (Reactant); RACT (Reactant or reagent)
 (synthesis and biol. properties of C12,13-cyclopropyl-epothilone A and
 related epothilones)

RN 213312-66-4 HCAPLUS

CN Oxacyclohexadecane-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-13-
 methylene-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-,
 (4S,7R,8S,9S,16S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
 Double bond geometry as shown.

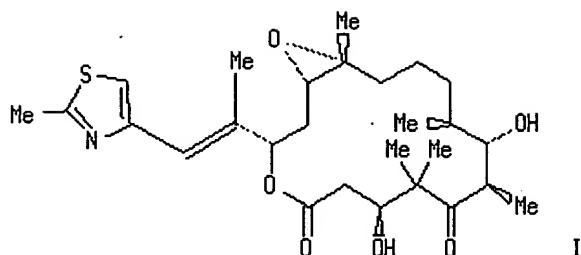


L12 ANSWER 9 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER: 1998:492150 HCAPLUS
 DOCUMENT NUMBER: 129:216449
 TITLE: Total synthesis of (-)-epothilone B
 AUTHOR(S): May, Scott A.; Grieco, Paul A.
 CORPORATE SOURCE: Department of Chemistry and Biochemistry, Montana
 State University, Bozeman, MT, 59717, USA
 SOURCE: Chemical Communications (Cambridge) (1998), (15),
 1597-1598

PUBLISHER: CODEN: CHCOFS; ISSN: 1359-7345
DOCUMENT TYPE: Royal Society of Chemistry
LANGUAGE: Journal
English
GI



AB The sixteen-membered ring macrolide (-)-epothilone B (I) has been synthesized by a route which features stereospecific methylation of an (E)- γ,δ -epoxy acrylate, the use of a double asym. reaction employing (R,R)-diisopropyltartrate and (E)-crotylboronate, ring closure by means of an olefin metathesis reaction.

IT 189453-10-9P

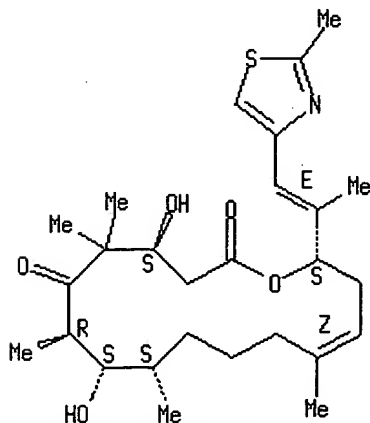
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(total synthesis of (-)-epothilone B)

RN 189453-10-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L12 ANSWER 10 OF 34 HCAPLUS COPYRIGHT 2002 ACS

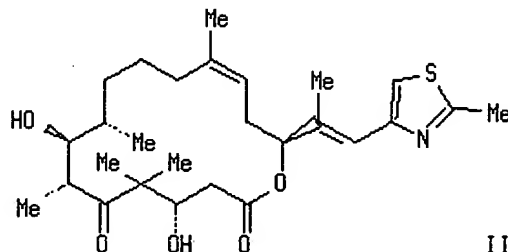
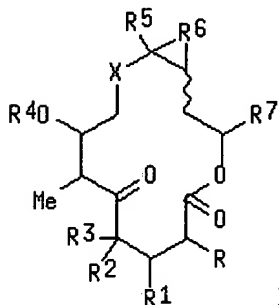
Full Text	Citing References
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ACCESSION NUMBER:	1998:405952 HCAPLUS
DOCUMENT NUMBER:	129:81625
TITLE:	Preparation of epothilone analogs as anticancer agents
INVENTOR(S):	Nicolaou, Costa Kyriacos; He, Yun; Ninkovic, Sacha; Pastor, Joaquin; Roschangar, Frank; Sarabia, Francisco; Vallberg, Hans; Vourloumis, Dionisios; Winssinger, Nicolas; Yang, Zhen; King, Nigel Paul; et al.
PATENT ASSIGNEE(S):	Novartis A.-G., Switz.; Scripps Research Institute
SOURCE:	PCT Int. Appl., 213 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
<u>WO 9825929</u>	<u>A1</u>	<u>19980618</u>	<u>WO 1997-EP7011</u>	<u>19971212</u>
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
<u>AU 9857577</u>	<u>A1</u>	<u>19980703</u>	<u>AU 1998-57577</u>	<u>19971212</u>
<u>AU 746597</u>	B2	20020502		
<u>EP 944634</u>	A1	19990929	<u>EP 1997-953808</u>	19971212
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
<u>BR 9714140</u>	A	20000229	<u>BR 1997-14140</u>	19971212
<u>CN 1246862</u>	A	20000308	<u>CN 1997-181771</u>	19971212
<u>JP 2001504856</u>	T2	20010410	<u>JP 1998-526247</u>	19971212
<u>PRIORITY APPLN. INFO.:</u>			<u>US 1996-32864P</u>	P 19961213
			<u>US 1997-856533</u>	A 19970514
			<u>US 1997-923869</u>	A2 19970904
			<u>WO 1997-EP7011</u>	W 19971212

OTHER SOURCE(S): MARPAT 129:81625
GI



AB Epothilone A, epothilone B, analogs of epothilone and libraries of epothilone analogs of formula I [X = (CH₂)_n; n = 1-5; R₁ = OH, OMe, absent; R₂, R₃ = H, CH₂, Me; R₄ = H, Me, protecting group; R₅ = H, Me, CHO, (substituted) CO₂H, etc.; R₆ = O, CH₂, absent; R₇ = thiazolealkyl, etc.] are synthesized. Epothilone A and B are known anticancer agents that derive their anticancer activity by the prevention of mitosis through the induction and stabilization of microtubulin assembly. Several of the analogs are demonstrated to have a superior cytotoxic activity as compared to epothilone A or epothilone B as demonstrated by their enhanced ability to induce the polymn. and stabilization of microtubules. Thus, II was prepd. and was shown to induce tubulin polymn. at 94% relative to GTP, and inhibit carcinoma cell growth.

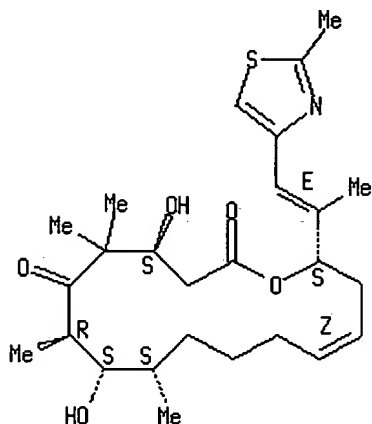
IT 186692-73-9P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of epothilone analogs as anticancer agents)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-
[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-
(9CI) (CA INDEX NAME)

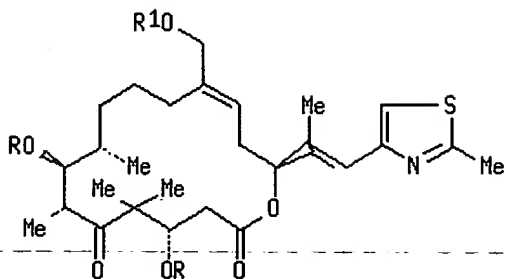
Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L12 ANSWER 11 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER:	1998:378435 HCAPLUS
DOCUMENT NUMBER:	129:189151
TITLE:	Total synthesis of 26-hydroxy-epothilone B and related analogs via a macrolactonization based strategy
AUTHOR(S):	Nicolaou, K. C.; Finlay, M. Ray V.; Ninkovic, Sacha; Sarabia, Francisco
CORPORATE SOURCE:	Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE:	Tetrahedron (1998), 54(25), 7127-7166 CODEN: TETRAB; ISSN: 0040-4020
PUBLISHER:	Elsevier Science Ltd.
DOCUMENT TYPE:	Journal
LANGUAGE:	English
OTHER SOURCE(S):	CASREACT 129:189151
GI	



AB The chem. synthesis of a series of 26-substituted epothilones B was described. Fully protected 26-hydroxydesoxy-epothilone B I (R = SiMe₂CMe₃, R1 = CPh₃), prepd. via a macrolactonization strategy, served as a common precursor to the designed epothilones described. The synthesized compds. were members of a large epothilone library of a no. of antitumor agents.

IT 198475-04-6P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT

(Reactant or reagent)

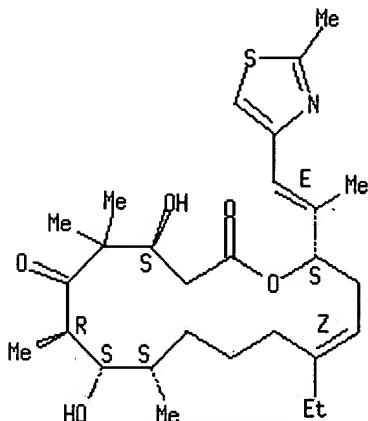
(total synthesis of 26-hydroxy-epothilone B and related analogs via a macrolactonization based strategy)

RN 198475-04-6 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 13-ethyl-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

Double bond geometry as shown.



L12 ANSWER 12 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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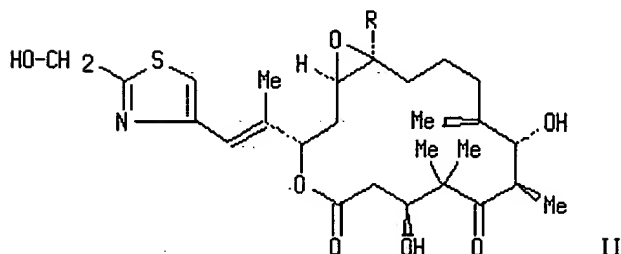
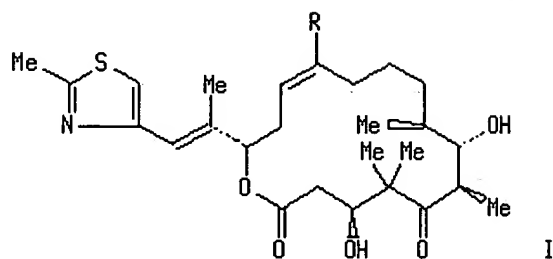
ACCESSION NUMBER: 1998:352834 HCAPLUS
DOCUMENT NUMBER: 129:53436
TITLE: Epothilone C, D, E and F, production process, and their use as cytostatics well as phytosanitary agents
INVENTOR(S): Reichenbach, Hans; Hofle, Gerhard; Gerth, Klaus; Steinmetz, Heinrich
PATENT ASSIGNEE(S): Gesellschaft Fur Biotechnologische Forschung m.b.H. (GBF), Germany; Reichenbach, Hans; Hofle, Gerhard; Gerth, Klaus; Steinmetz, Heinrich
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
<u>WO 9822461</u>	<u>A1</u>	<u>19980528</u>	<u>WO 1997-EP6442</u>	<u>19971118</u>
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
<u>AU 9854837</u>	<u>A1</u>	<u>19980610</u>	<u>AU 1998-54837</u>	<u>19971118</u>
<u>ZA 9710384</u>	<u>A</u>	<u>19990518</u>	<u>ZA 1997-10384</u>	<u>19971118</u>
<u>EP 941227</u>	<u>A1</u>	<u>19990915</u>	<u>EP 1997-951233</u>	<u>19971118</u>
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
<u>CN 1237970</u>	<u>A</u>	<u>19991208</u>	<u>CN 1997-199814</u>	<u>19971118</u>
<u>BR 9713363</u>	<u>A</u>	<u>20000125</u>	<u>BR 1997-13363</u>	<u>19971118</u>

JP 2001504474 T2 20010403
 TW 408119 B 20001011
 NO 9902338 A 19990514
 KR 2000053308 A 20000825
 PRIORITY APPLN. INFO.:

JP 1998-523208 19971118
 TW 1997-86117334 19980121
 NO 1999-2338 19990514
 KR 1999-704302 19990514
 DE 1996-19647580 A 19961118
 DE 1997-19707506 A 19970225
 WO 1997-EP6442 W 19971118

GI



AB The present invention concerns the epothilones, esp. epothilone C [I; R = H] and epothilone D [I; R = Me] as well as epothilone E [II; R = H] and epothilone F [II; R = Me], the prodn. process, and their application for producing therapeutic agents, including cytostatic agents as well as phytosanitary agents.

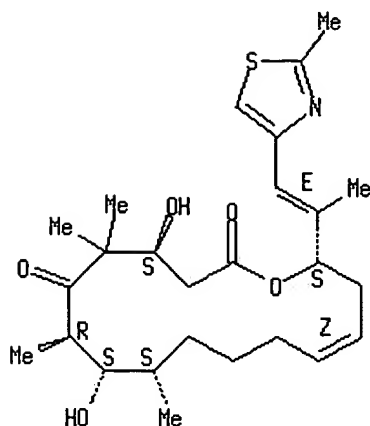
IT **186692-73-9P**, Epothilone C

RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses) (epothilone C, D, E and F, prodn. process, and use as cytostatics well as phytosanitary agents)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
 Double bond geometry as shown.



L12 ANSWER 13 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER: 1998:163596 HCAPLUS
DOCUMENT NUMBER: 128:217229
TITLE: Method for producing epothilones and the intermediate products obtained during the production process
INVENTOR(S): Schinzer, Dieter; Limberg, Anja; Bohm, Oliver M.; Bauer, Armin; Cordes, Martin
PATENT ASSIGNEE(S): Novartis Aktiengesellschaft, Switz.; Schinzer, Dieter; Limberg, Anja; Bohm, Oliver M.; Bauer, Armin; Cordes, Martin
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
<u>WO 9808849</u>	<u>A1</u>	<u>19980305</u>	<u>WO 1997-DE111</u>	<u>19970115</u>
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
<u>DE 19636343</u>	<u>C1</u>	<u>19971023</u>	<u>DE 1996-19636343</u>	<u>19960830</u>
<u>DE 19645361</u>	<u>A1</u>	<u>19980430</u>	<u>DE 1996-19645361</u>	<u>19961028</u>
<u>DE 19645362</u>	<u>A1</u>	<u>19980430</u>	<u>DE 1996-19645362</u>	<u>19961028</u>
<u>AU 9721493</u>	<u>A1</u>	<u>19980319</u>	<u>AU 1997-21493</u>	<u>19970115</u>
<u>AU 716610</u>	<u>B2</u>	<u>20000302</u>		
<u>EP 923583</u>	<u>A1</u>	<u>19990623</u>	<u>EP 1997-914077</u>	<u>19970115</u>
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
<u>JP 2001500851</u>	<u>T2</u>	<u>20010123</u>	<u>JP 1998-511141</u>	<u>19970115</u>
PRIORITY APPLN. INFO.:			<u>DE 1996-19636343</u>	<u>A 19960830</u>
			<u>DE 1996-19645361</u>	<u>A 19961028</u>
			<u>DE 1996-19645362</u>	<u>A 19961028</u>
			<u>WO 1997-DE111</u>	<u>W 19970115</u>

OTHER SOURCE(S): CASREACT 128:217229; MARPAT 128:217229
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB A method for producing epothilones I [R = H (A), Me (B)] is characterized by reaction of thiazole II with carboxylic acid III (B = CH₂Ph, THP, silyl protecting group; R = H, Me), followed by olefin metathesis in the presence of a noble metal catalyst, hydroxyl deprotection and epoxidn. Thus, epothilone A (I; R = H) was prepd. via acylation of II with III (R = H, B = SiMe₂CMe₃) in CH₂Cl₂ contg. DCC and DMAP, followed by olefin metathesis in CH₂Cl₂ contg. catalytic benzylidenebis(tricyclohexylphosphine)ruthenium dichloride, desilylation with aq. HF in Et₂O/MeCN and epoxidn. with dimethyldioxirane in acetone. Epothilones A and B are natural substances which are produced by microorganisms and have similar properties to those of taxol and, therefore, are of interest to the pharmaceutical chem.

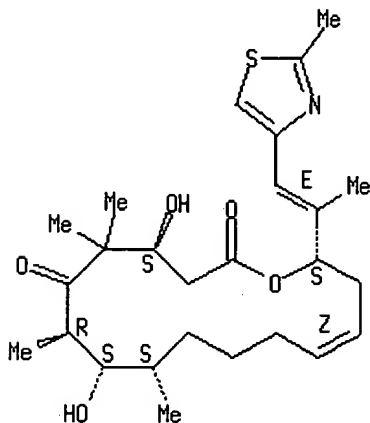
IT **186692-73-9P**, Epothilone C

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of epothilones via olefin metathesis)

RN **186692-73-9** HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L12 ANSWER 14 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER:	1998:121923 HCAPLUS
DOCUMENT NUMBER:	128:252599
TITLE:	Farnesyl transferase inhibitors cause enhanced mitotic sensitivity to taxol and epothilones
AUTHOR(S):	Moasser, Mark M.; Sepp-Lorenzino, Laura; Kohl, Nancy E.; Oliff, Allen; Balog, Aaron; Su, Dai-Shi; Danishefsky, Samuel J.; Rosen, Neal
CORPORATE SOURCE:	Department of Medicine, Memorial Sloan-Kettering Cancer Center, Sloan-Kettering Institute, New York, NY, 10021, USA
SOURCE:	Proceedings of the National Academy of Sciences of the United States of America (1998), 95(4), 1369-1374 CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER:	National Academy of Sciences
DOCUMENT TYPE:	Journal
LANGUAGE:	English
AB	An important class of cellular proteins, which includes members of the p21ras family, undergoes post-translational farnesylation, a modification

required for their partition to membranes. Specific farnesyl transferase inhibitors (FTIs) have been developed that selectively inhibit the processing of these proteins. FTIs have been shown to be potent inhibitors of tumor cell growth in cell culture and in murine models and at doses that cause little toxicity to the animal. These data suggest that these drugs might be useful therapeutic agents. We now report that, when FTI is combined with some cytotoxic antineoplastic drugs, the effects on tumor cells are additive. No interference is noted. Furthermore, FTI and agents that prevent microtubule depolymn., such as taxol or epothilones, act synergistically to inhibit cell growth. FTI causes increased sensitivity to induction of metaphase block by these agents, suggesting that a farnesylated protein may regulate the mitotic check point. The findings imply that FTI may be a useful agent for the treatment of tumors with wild-type ras that are sensitive to taxanes.

IT **186692-73-9**, Desoxyepothilone A

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

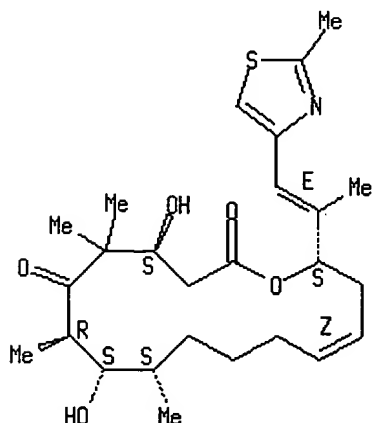
(farnesyl transferase inhibitors cause enhanced mitotic sensitivity to taxol and epothilones)

RN **186692-73-9** HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

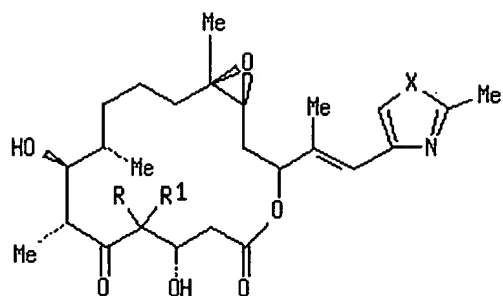
Double bond geometry as shown.



L12 ANSWER 15 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER:	1998:50907 HCAPLUS
DOCUMENT NUMBER:	128:180246
TITLE:	Total synthesis of oxazole- and cyclopropane-containing epothilone B analogs by the macrolactonization approach
AUTHOR(S):	Nicolaou, K. C.; Sarabia, Francisco; Finlay, M. Ray V.; Ninkovic, Sacha; King, N. Paul; Vourloumis, Dionisios; He, Yun
CORPORATE SOURCE:	Department of Chemistry and The Skaggs Institute for Chemical Biology The Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE:	Chemistry--A European Journal (1997), 3(12), 1971-1986 CODEN: CEUJED; ISSN: 0947-6539
PUBLISHER:	Wiley-VCH Verlag GmbH
DOCUMENT TYPE:	Journal
LANGUAGE:	English
GI	



AB In order to probe structure-activity relationships in the epothilone area, two series of epothilone B analogs were designed and synthesized. The first series contg. an oxazole moiety in place of a thiazole on the side chain was constructed via utilization of key intermediates whereas the second series contg. an ethano group instead of the gem-di-Me group at position 4 was synthesized. A Yamaguchi-type macrolactonization reaction was used to construct the macrocycle from a secoacid, which was assembled, in both cases, via a) an aldol reaction, b) an Enders alkylation, and c) a Wittig-type reaction. This convergent strategy provided access to oxazole and 4,4-ethano analogs, e.g., I (R = R1 = Me, X = O, S; RR1 = CH2CH2, X = O, S).

IT 198571-09-4P

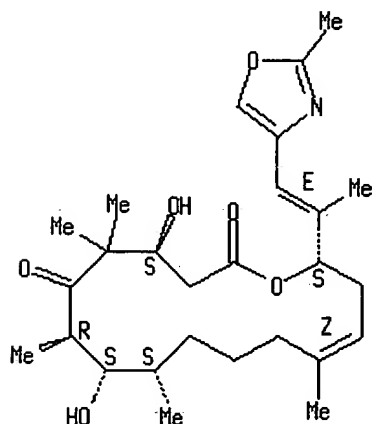
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(total synthesis of oxazole- and cyclopropane-contg. epothilone B analogs via macrolactonization)

RN 198571-09-4 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[(1E)-1-methyl-2-(2-methyl-4-oxazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



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L12 ANSWER 16 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
ACCESSION NUMBER:	1998:50906 HCAPLUS
DOCUMENT NUMBER:	128:140541
TITLE:	Total synthesis of oxazole- and cyclopropane-containing epothilone A analogs by the olefin metathesis approach
AUTHOR(S):	Nicolaou, K. C.; Vallberg, Hans; King, N. Paul; Roschangar, Frank; He, Yun; Vourloumis, Dionisios;

ACCESSION NUMBER:

1998:50906 HCAPLUS

DOCUMENT NUMBER:

128:140541

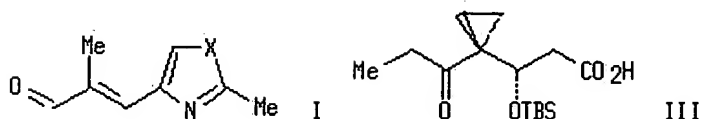
TITLE:

Total synthesis of oxazole- and cyclopropane-containing epothilone A analogs by the olefin metathesis approach

AUTHOR(S):

Nicolaou, K. C.; Vallberg, Hans; King, N. Paul; Roschangar, Frank; He, Yun; Vourloumis, Dionisios;

Nicolaou, Christopher G.
 CORPORATE SOURCE: Department of Chemistry and The Skaggs Institute for
 Chemical Biology, The Scripps Research Institute, La
 Jolla, CA, 92037, USA
 SOURCE: Chemistry--A European Journal (1997), 3(12), 1957-1970
 CODEN: CEUJED; ISSN: 0947-6539
 PUBLISHER: Wiley-VCH Verlag GmbH
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 GI



AB For structure-activity relationship studies, two series of epothilone A analogs have been designed and synthesized, one contg. an oxazole moiety instead of the thiazole heterocycle and the other contg. a spirocyclopropane moiety in place of the gem-di-Me group at position C-4 (4,4-ethano-epothilones). The olefin metathesis strategy in soln. was utilized for the chem. synthesis of these compds. starting with key building blocks (I) (X = O), (S)-H₂C=CH(CH₂)₃CH(Me)CHO (II), (S)-MeCH₂COCMe₂CH(OSiMe₂CMe₃)CH₂CO₂H for the oxazole series and building blocks I (X = S), II, and (III) for the 4,4-ethano series. The convergent strategy towards the designed epothilone A series involved: a- an aldol condensation reaction, b- an esterification reaction, c- an olefin metathesis reaction catalyzed by [RuCl₂(=CHPh)-(PCy₃)₂], and d- epoxidn. of the macrocycle double bond.

IT 198475-12-6P

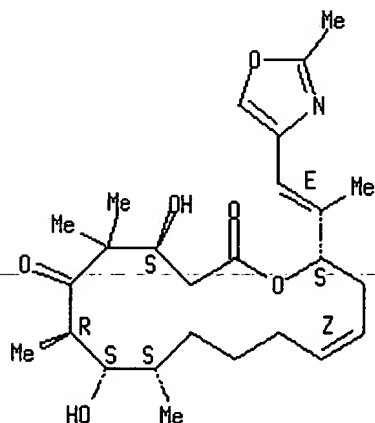
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(total synthesis of oxazole- and cyclopropane-contg. epothilone A analogs by the olefin metathesis approach)

RN 198475-12-6 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-oxazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
 Double bond geometry as shown.



L12 ANSWER 17 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text Citing
 Text References

ACCESSION NUMBER: 1998:729 HCAPLUS
 DOCUMENT NUMBER: 128:88685
 TITLE: Metathesis vs metastasis: the chemistry and biology of the epothilones
 AUTHOR(S): Finlay, Ray
 CORPORATE SOURCE: Dep. Chemistry, The Skaggs Inst. for Chemical Biol., The Scripps Res. Inst., La Jolla, CA, 92037, USA
 SOURCE: Chemistry & Industry (London) (1997), (24), 991-996
 CODEN: CHINAG; ISSN: 0009-3068
 PUBLISHER: Society of Chemical Industry
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: English

AB A review with 15 refs. on a recent entry onto the scene of potentially useful natural products, the epothilones A - E, providing valuable information for the fight against cancer via their interaction with microtubules.

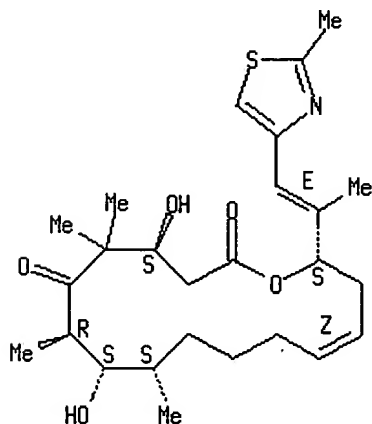
IT **186692-73-9P**, Epothilone C

RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); USES (Uses)
 (chem. and bioactivity of the epothilones)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
 Double bond geometry as shown.

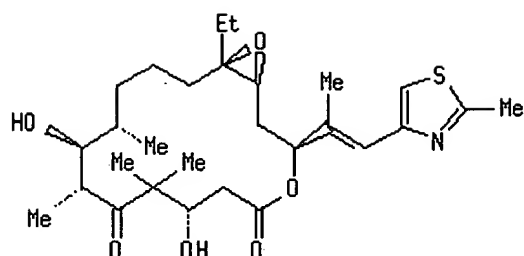


L12 ANSWER 18 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER: 1997:787450 HCAPLUS
 DOCUMENT NUMBER: 128:101936
 TITLE: Total synthesis of 26-hydroxyepothilone B and related analogs
 AUTHOR(S): Nicolaou, K. C.; Ninkovic, Sacha; Finlay, M. Ray V.; Sarabia, Francisco; Li, Tianhu
 CORPORATE SOURCE: Department of Chemistry and Biochemistry, University of California, California, 92093, USA
 SOURCE: Chemical Communications (Cambridge) (1997), (24), 2343-2344
 CODEN: CHCOFS; ISSN: 1359-7345
 PUBLISHER: Royal Society of Chemistry
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 OTHER SOURCE(S): CASREACT 128:101936

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I

AB A series of 26-substituted epothilones B, e.g. I, were constructed by total synthesis involving a selective Wittig olefination, an aldol reaction and a macrolactonization as key steps.

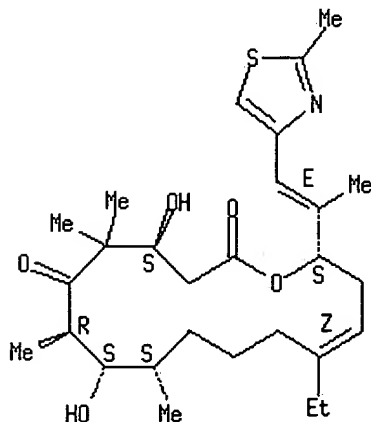
IT 198475-04-6P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent) (total synthesis of 26-hydroxyepothilone B and related analogs)

RN 198475-04-6 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 13-ethyl-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L12 ANSWER 19 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full
Text

Citing
References

ACCESSION NUMBER: 1997:724919 HCAPLUS

DOCUMENT NUMBER: 127:346221

TITLE: Synthesis of epothilones A and B in solid and solution phase. [Erratum to document cited in CA127:4950]

AUTHOR(S): Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Ninkovic, S.; Sarabia, F.; He, Y.; Vourloumis, D.; Yang, Z.; Li, T.; Giannakakou, P.; Hamel, E.

CORPORATE SOURCE: Dep. Chemistry, Skaggs Inst. Chem. Biology, Scripps Res. Inst., La Jolla, CA, 92037, USA

SOURCE: Nature (London) (1997), 390(6655), 100

CODEN: NATUAS; ISSN: 0028-0836

PUBLISHER: Macmillan Magazines

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Ref. 19, includes, in addn. to a total synthesis of epothilone B, biol.

data for compd. 23 and other congeners similar to the reported in the Letter.

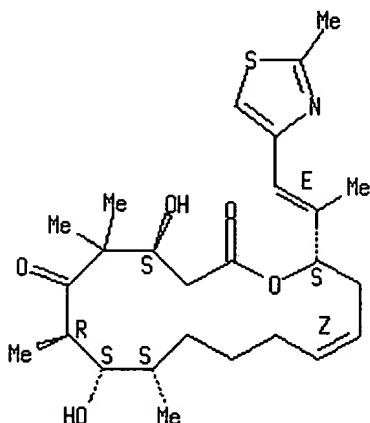
IT 186692-73-9P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent) (prepn. of a combinatorial library via solid-phase synthesis of epothilone A and soln.-phase synthesis of epothilone B (Erratum))

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L12 ANSWER 20 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER: 1997:714315 HCAPLUS
DOCUMENT NUMBER: 128:3560
TITLE: Designed epothilones: combinatorial synthesis, tubulin assembly properties, and cytotoxic action against taxol-resistant tumor cells
AUTHOR(S): Nicolaou, K. C.; Vourloumis, Dionisios; Li, Tianhu; Pastor, Joaquin; Winssinger, Nicolas; He, Yun; Ninkovic, Sacha; Sarabia, Francisco; Vallberg, Hans; Roschangar, Frank; King, N. Paul; Finlay, M. Ray V.; Giannakakou, Pareskevi; Verdier-Pinard, Pascal; Hamel, Ernest
CORPORATE SOURCE: Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: Angewandte Chemie, International Edition in English (1997), 36(19), 2097-2103
CODEN: ACIEAY; ISSN: 0570-0833
PUBLISHER: Wiley-VCH
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The title work demonstrates the power of interfacing combinatorial chem. with chem. biol. as facilitated by solid-phase synthesis, radiofrequency encoded combinatorial chem. and modern biol. assays. A library of 112 epothilones were prepd. by solid-phase synthesis, their structure activity relationships measured by tubulin binding assay and some tested for inhibition of carcinoma cell growth.

IT 186692-73-9P

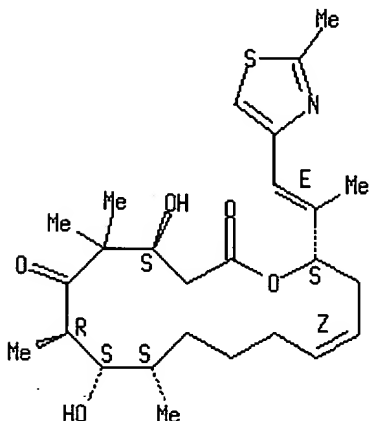
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);

BIOL (Biological study); PREP (Preparation); USES (Uses)
(combinatorial synthesis of epothilone library, tubulin assembly
properties, and cytotoxic action against taxol-resistant tumor cells)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-
[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-
(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L12 ANSWER 21 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER: 1997:714314 HCAPLUS
DOCUMENT NUMBER: 127:358730
TITLE: Structure-activity relationships of the epothilones
and the first in vivo comparison with paclitaxel
AUTHOR(S): Su, Dai-Shi; Balog, Aaron; Meng, Dongfang; Bertinato,
Peter; Danishefsky, Samuel J.; Zheng, Yu-Huang; Chou,
Ting-Chao; He, Lifeng; Horwitz, Susan B.
CORPORATE SOURCE: Laboratory for Bioorganic Chemistry, Sloan-Kettering
Institute for Cancer Research, New York, NY, 10021,
USA
SOURCE: Angewandte Chemie, International Edition in English
(1997), 36(19), 2093-2096
CODEN: ACIEAY; ISSN: 0570-0833
PUBLISHER: Wiley-VCH
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The structure-activity relationships of the epothilones and 18 derivs. and
analogues were studied. An in vivo comparison of the chemotherapeutic
effect of epothilone B with that of paclitaxel was also studied. The
chemotherapeutic effect of daily doses of epothilone B (0.7 mg/kg) and
paclitaxel (2 mg/kg) in CB-17 SCID mice bearing drug-resistant human
CCRF-CEM/VBL xenografts were T/C = 0.33 and T/C = 0.70, resp.

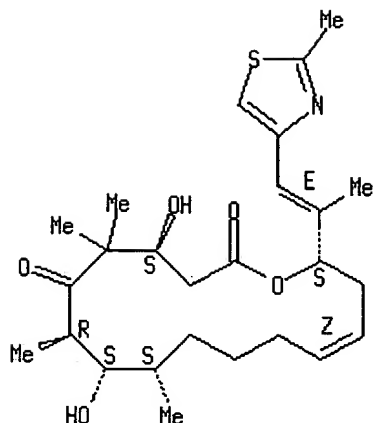
IT 186692-73-9, Desoxyepothilone A

RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); BIOL (Biological study)
(structure-activity relationships of the epothilones and in vivo
comparison with paclitaxel)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-
[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-
(9CI) (CA INDEX NAME)

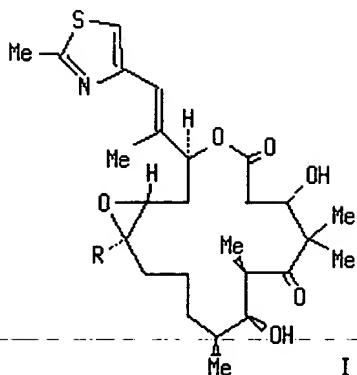
Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L12 ANSWER 22 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER:	1997:665094 HCAPLUS
DOCUMENT NUMBER:	127:293040
TITLE:	Total Syntheses of Epothilones A and B
AUTHOR(S):	Meng, Dongfang; Bertinato, Peter; Balog, Aaron; Su, Dai-Shi; Kamenecka, Ted; Sorensen, Erik; Danishefsky, Samuel J.
CORPORATE SOURCE:	Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, New York, NY, 10021, USA
SOURCE:	Journal of the American Chemical Society (1997), 119(42), 10073-10092 CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER:	American Chemical Society
DOCUMENT TYPE:	Journal
LANGUAGE:	English
OTHER SOURCE(S):	CASREACT 127:293040
GI	



AB Convergent, stereocontrolled total syntheses of the microtubule-stabilizing macrolides epothilones A (I; R = H) and B (I; R = Me) have been achieved. Four distinct ring-forming strategies were pursued. Of these four, three were reduced to practice. In one approach, the action of a base on a substance possessing an acetate ester and a nonenolizable aldehyde brought about a remarkably effective macroaldolization simultaneously creating the C2-C3 bond and the hydroxyl-bearing

stereocenter at C-3. Alternatively, the 16-membered macrolide of the epothilones could be fashioned through a C12-C13 ring-closing olefin metathesis and through macrolactonization of the appropriate hydroxy acid. The application of a stereospecific B-alkyl Suzuki coupling strategy permitted the establishment of a cis C12-C13 olefin, thus setting the stage for an eventual site- and diastereoselective epoxidn. reaction. The development of a novel cyclopropane solvolysis strategy for incorporating the geminal Me groups of the epothilones, and the use of Lewis acid catalyzed diene-aldehyde cyclocondensation (LACDAC) and asym. allylation methodol. are also noteworthy.

IT **186692-73-9P**, (-)-Desoxyepothilone A

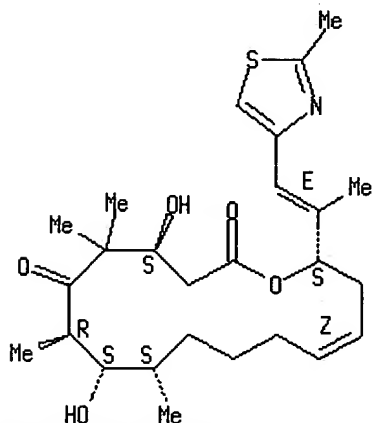
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(syntheses of epothilones A and B via macroaldolization, olefin metathesis and macrolactonization)

RN **186692-73-9** HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L12 ANSWER 23 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER:	1997:528753 HCAPLUS
DOCUMENT NUMBER:	127:135660
TITLE:	Total Syntheses of Epothilones A and B via a Macrolactonization-Based Strategy
AUTHOR(S):	Nicolaou, K. C.; Ninkovic, S.; Sarabia, F.; Vourloumis, D.; He, Y.; Vallberg, H.; Finlay, M. R. V.; Yang, Z.
CORPORATE SOURCE:	Department of Chemistry and The Skaggs, Institute for Chemical Biology, La Jolla, CA, 92037, USA
SOURCE:	Journal of the American Chemical Society (1997), 119(34), 7974-7991
PUBLISHER:	CODEN: JACSAT; ISSN: 0002-7863
DOCUMENT TYPE:	American Chemical Society
LANGUAGE:	Journal
OTHER SOURCE(S):	English
GI	CASREACT 127:135660

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The total syntheses of epothilones A (I) (R = H) and B I (R = Me) and several analogs are described. The reported strategy relies on a macrolactonization approach and features selective epoxidn. of the macrocycle double bond in precursors II (R = H, Me) as well as high convergency and flexibility. Building blocks (S)-MeCH₂COC(Me)2CH(OSiMe₂CMe₃)CH₂CO₂H, (S)-Me₃CMe₂SiOCH₂CH(Me)CH₂CH₂CH₂COR (R = H, Me), (III) [R₂ = CH₂CH₂P+(Ph)3I-; CH₂CHO] were constructed by asym. processes and coupled via Wittig, aldol, and macrolactonization reactions to afford the basic skeleton of epothilones and that of several of their analogs by a relatively short route. The utilization of intermediate III [R₂ = (E)-CH₂CH=C(Me)CH₂CH₂CH₂I], obtained via a stereoselective Wittig reaction and its Enders coupling to SAMP hydrazone, in combination with a stereoselective aldol reaction with the modified substrate (S)-MeCH₂COC(Me)2CH(OSiMe₂CMe₃)CH₂CH₂OSiMe₂CMe₃ improved the stereoselectivity and efficiency of the total synthesis of these new and highly potent microtubule binding antitumor agents.

IT **186692-73-9P**

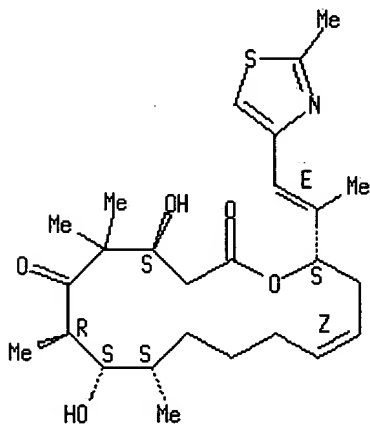
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(total syntheses of epothilones A and B via a macrolactonization-based strategy)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L12 ANSWER 24 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER:	1997:528752 HCAPLUS
DOCUMENT NUMBER:	127:149021
TITLE:	The Olefin Metathesis Approach to Epothilone A and Its Analogs
AUTHOR(S):	Nicolaou, K. C.; He, Y.; Vourloumis, D.; Vallberg, H.; Roschangar, F.; Sarabia, F.; S.Ninkovic; Yang, Z.; Trujillo, J. I.
CORPORATE SOURCE:	Department of Chemistry and The Skaggs, Institute for Chemical Biology, La Jolla, CA, 92037, USA
SOURCE:	Journal of the American Chemical Society (1997), 119(34), 7960-7973
PUBLISHER:	CODEN: JACSAT; ISSN: 0002-7863
DOCUMENT TYPE:	American Chemical Society
LANGUAGE:	Journal
	English

OTHER SOURCE(S): CASREACT 127:149021

GI For diagram(s), see printed CA Issue.

AB The olefin metathesis approach to epothilone A (I) and several diastereomeric analogs is described. Key building blocks II, (S)-OHCH(Me)CH₂CH₂CH=CH₂, and (S)-MeCH₂COC(Me)₂CH(OSiMe₂CMe₃)CH₂CO₂H were constructed in optically active form and were coupled and elaborated to olefin metathesis precursor III (R = SiMe₂CMe₃) via an aldol reaction and an esterification coupling. Olefin metathesis of compd. III (R = SiMe₂CMe₃), under the catalytic influence of RuCl₂(:CHPh)(PCy₃)₂, furnished cis- and trans-cyclic olefins IV (R = SiMe₂CMe₃). Epoxidn. of (Z)-IV (R = H) gave I and several analogs, whereas epoxidn. of (E)-IV (R = H) resulted in addnl. epothilones. Similar elaboration of isomeric as well as simpler intermediates resulted in yet another series of epothilone analogs and model systems.

IT **186692-73-9P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

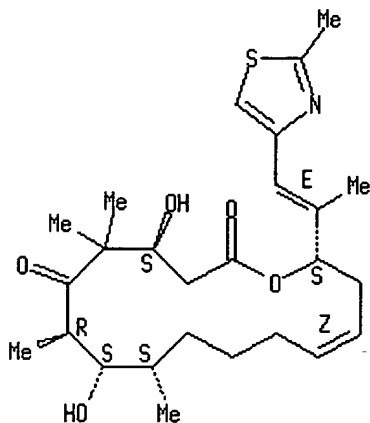
(synthesis of epothilone A and analogs via olefin metathesis)

RN **186692-73-9** HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

Double bond geometry as shown.



L12 ANSWER 25 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER: 1997:456769 HCAPLUS

DOCUMENT NUMBER: 127:50474

TITLE: Preparation of epothilone derivatives as agrochemicals and pharmaceuticals

INVENTOR(S): Hoefle, Gerhard; Kiffe, Michael

PATENT ASSIGNEE(S): Gesellschaft fuer Biotechnologische Forschung MbH (Gbf), Germany

SOURCE: Ger. Offen., 9 pp.

CODEN: GWXXBX

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

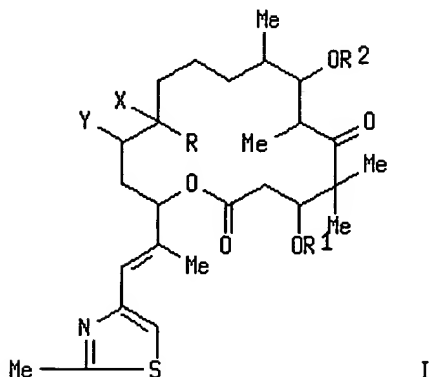
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19542986	A1	19970522	DE 1995-19542986	19951117
WO 9719086	A1	19970529	WO 1996-EP5080	19961118
W: JP, US				

RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
EP 873341 A1 19981028 EP 1996-939097 19961118
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, FI
EP 903348 A1 19990324 EP 1998-121523 19961118
EP 903348 B1 20020605
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, FI
JP 2000500757 T2 20000125 JP 1997-519381 19961118
EP 1186606 A1 20020313 EP 2001-127352 19961118
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, FI
AT 218556 E 20020615 AT 1998-121523 19961118
US 6288237 B1 20010911 US 1998-77055 19980803
US 2001034452 A1 20011025 US 2001-836134 20010416

PRIORITY APPLN. INFO.:

DE 1995-19542986 A 19951117
DE 1996-19639456 A 19960925
EP 1996-939097 A3 19961118
WO 1996-EP5080 W 19961118
US 1998-77055 A3 19980803

OTHER SOURCE(S): MARPAT 127:50474
 GI



AB The title compds., e.g., I [R = H, C1-4 alkyl; R1, R2 = H, C1-6 alkyl, C1-6 acyl, benzoyl, C1-4 trialkylsilyl, benzyl, Ph, C1-6 alkoxy, C6 alkyl-, hydroxy-, and halo-substituted benzyl or phenyl; X, Y = halo, OH, acyloxy, alkoxy, benzoyloxy], useful as agrochems. and pharmaceuticals (no data), are prepd. Thus, epothilone A in acetone contg. trifluoroacetic acid was heated overnight at 50° and the reaction mixt. was adjusted to pH 7 with 1 M phosphate buffer to give 2 isomers, each in 19% yield.

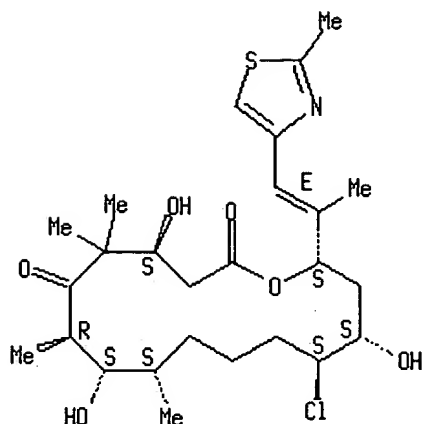
IT 191105-82-5P

RL: AGR (Agricultural use); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
 (prepn. of epothilone derivs. as agrochems. and pharmaceuticals)

RN 191105-82-5 HCAPLUS

CN Oxacyclohexadecane-2,6-dione, 13-chloro-4,8,14-trihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, [4R*,7S*,8R*,9R*,13R*,14R*,16R*(E)]- (9CI) (CA INDEX NAME)

Relative stereochemistry.
 Double bond geometry as shown.

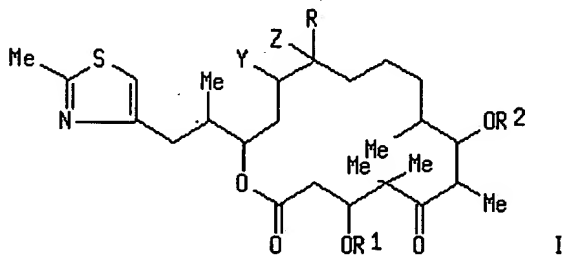


L12 ANSWER 26 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER: 1997:443365 HCAPLUS
 DOCUMENT NUMBER: 127:81289
 TITLE: Preparation of epothilone derivatives as agrochemicals and pharmaceuticals
 INVENTOR(S): Hofle, Gerhard; Kiffe, Michael
 PATENT ASSIGNEE(S): Gesellschaft Fur Biotechnologische Forschung Mbh (Gbf), Germany; Hofle, Gerhard; Kiffe, Michael
 SOURCE: PCT Int. Appl., 38 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: German
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
<u>WO 9719086</u>	A1	19970529	<u>WO 1996-EP5080</u>	19961118
W: JP, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
<u>DE 19542986</u>	A1	19970522	<u>DE 1995-19542986</u>	19951117
<u>DE 19639456</u>	A1	19980326	<u>DE 1996-19639456</u>	19960925
<u>EP 873341</u>	A1	19981028	<u>EP 1996-939097</u>	19961118
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
<u>JP 2000500757</u>	T2	20000125	<u>JP 1997-519381</u>	19961118
<u>US 6288237</u>	B1	20010911	<u>US 1998-77055</u>	19980803
PRIORITY APPLN. INFO.:			<u>DE 1995-19542986</u>	A 19951117
			<u>DE 1996-19639456</u>	A 19960925
			<u>WO 1996-EP5080</u>	W 19961118
OTHER SOURCE(S):		MARPAT 127:81289		
GI				



AB The title compds., e.g., I [R = H, C1-4 alkyl; R1, R2 = H, C1-6 alkyl, C1-6 acyl, benzoyl, C1-4 trialkylsilyl, benzyl, Ph, C1-6 alkoxy, C6 alkyl-, hydroxy-, and halo-substituted benzyl or phenyl; X, Y = H, halo, pseudohalo, OH, acyloxy, alkoxy, benzoyloxy; or YZ = O, bond; however, I may not be epothilone A or B], useful as agrochems. and pharmaceuticals (no data), are prepd. Thus, epothilone A in acetone contg. trifluoroacetic acid was heated overnight at 50° and the reaction mixt. was adjusted to pH 7 with 1 M phosphate buffer to give 2 isomers, each in 19% yield.

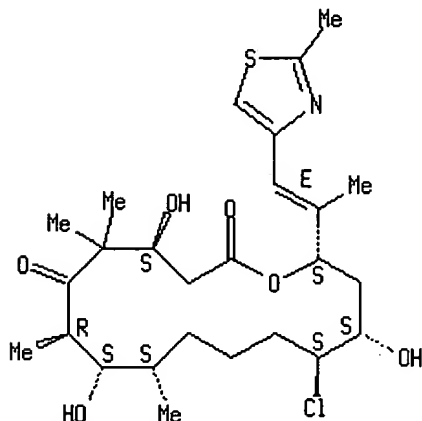
IT **191105-82-5P**

RL: AGR (Agricultural use); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of epothilone derivs. as agrochems. and pharmaceuticals)

RN **191105-82-5** HCAPLUS

CN Oxacyclohexadecane-2,6-dione, 13-chloro-4,8,14-trihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, [4R*,7S*,8R*,9R*,13R*,14R*,16R*(E)]- (9CI) (CA INDEX NAME)

Relative stereochemistry.
Double bond geometry as shown.



L12 ANSWER 27 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER: 1997:430309 HCAPLUS

DOCUMENT NUMBER: 127:108793

TITLE: Stereoselective syntheses and evaluation of compounds in the 8-desmethylepothilone A series: some surprising observations regarding their chemical and biological properties

AUTHOR(S): Balog, Aaron; Betinato, Peter; Su, Dai-Shi; Meng, Dongfang; Sorensen, Erik; Danishefsky, Samuel J.; Zheng, Yu-Huang; Chou, Ting-Chao; He, Lifeng; Horwitz, Susan B.

CORPORATE SOURCE: Lab. Bioorganic Chem., Sloan-Kettering Inst. Cancer Res., New York, NY, 10021, USA

SOURCE: Tetrahedron Letters (1997), 38(26), 4529-4532
CODEN: TELEAY; ISSN: 0040-4039

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 127:108793

AB The title compds. have been synthesized in a convergent way by recourse to a Weiler type dianion construction.

IT **186692-73-9**, Desoxyepothilone A

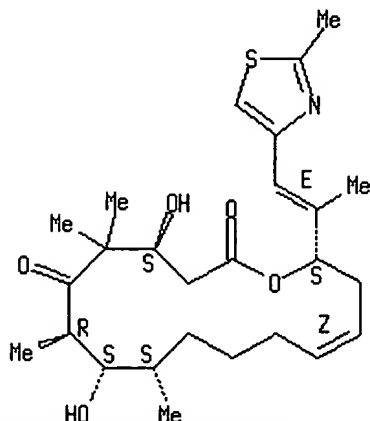
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); BIOL (Biological study)
(stereoselective syntheses and evaluation of compds. in the
8-desmethylepothilone A series)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-
[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-
(9CI) (CA INDEX NAME)

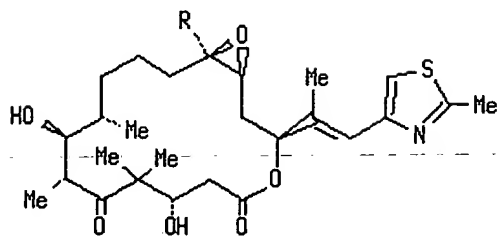
Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L12 ANSWER 28 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER: 1997:330310 HCAPLUS
DOCUMENT NUMBER: 127:4950
TITLE: Synthesis of epothilones A and B in solid and solution phase
AUTHOR(S): Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Ninkovic, S.; Sarabia, F.; He, Y.; Vourloumis, D.; Yang, Z.; Li, T.; Giannakakou, P.; Hamel, E.
CORPORATE SOURCE: Dep. Chemistry, Skaggs Inst. Chem. Biology, Scripps Res. Inst., La Jolla, CA, 92037, USA
SOURCE: Nature (London) (1997), 387(6630), 268-272
CODEN: NATUAS; ISSN: 0028-0836
PUBLISHER: Macmillan Magazines
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 127:4950
GI



I

AB Epothilones A (I; R = H) and B (I: R = Me), two compds. that were recently isolated from myxobacterium Sorangium cellulosum strain 90, have generated intense interest among chemists, biologists and clinicians owing to the structural complexity, unusual mechanism of interaction with microtubules and anticancer potential of these mols. Like taxol, they exhibit

cytotoxicity against tumor cells by inducing microtubule assembly and stabilization, even in taxol-resistant cell lines. Following the structural elucidation of these mols. by X-ray crystallog. in 1996, several synthesis of epothilones A and B have been reported, indicative of the potential importance of these mols. in the cancer field. Here we report the first solid-phase synthesis of epothilone A, the total synthesis of epothilone B, and the generation of a small epothilone library. The solid-phase synthesis applied here to epothilone A could open up new possibilities in natural-product synthesis and, together with soln.-phase synthesis of other epothilones, paves the way for the generation of large combinatorial libraries of these important mols. for biol. screening.

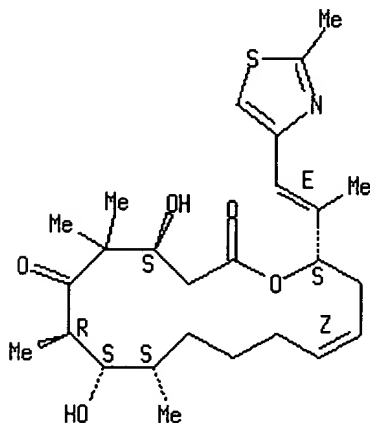
IT 186692-73-9P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent) (prepn. of a combinatorial library via solid-phase synthesis of epothilone A and soln.-phase synthesis of epothilone B)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L12 ANSWER 29 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER:	1997:302059 HCAPLUS
DOCUMENT NUMBER:	127:4948
TITLE:	Total synthesis of (-)-epothilone B: an extension of the Suzuki coupling method and insights into structure-activity relationships of the epothilones
AUTHOR(S):	Su, Dai-Shi; Meng, Dongfang; Bertinato, Peter; Balog, Aaron; Sorensen, Erik J.; Danishefsky, Samuel J.; Zheng, Yu-Huang; Chou, Ting-Chao; He, Lifeng; Horwitz, Susan B.
CORPORATE SOURCE:	Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, New York, NY, 10021, USA
SOURCE:	Angewandte Chemie, International Edition in English (1997), 36(7), 757-759 CODEN: ACIEAY; ISSN: 0570-0833
PUBLISHER:	VCH
DOCUMENT TYPE:	Journal
LANGUAGE:	English
OTHER SOURCE(S):	CASREACT 127:4948

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB (-)-Epothilone B (I; R = Me, X = O) and desoxyepothilone B (I; R = Me, X = bond) were prepd. via Suzuki coupling of (Z)-vinyl iodide II with borane III. I (R = H, Me, X = O, bond) and the E-isomers of I (R = H, Me, X = bond) were tested for efficacy against drug-sensitive and resistant CCRF-CEM cell lines (IC50 = 0.0004 - 0.262 µM).

IT **186692-73-9**, Desoxyepothilone A

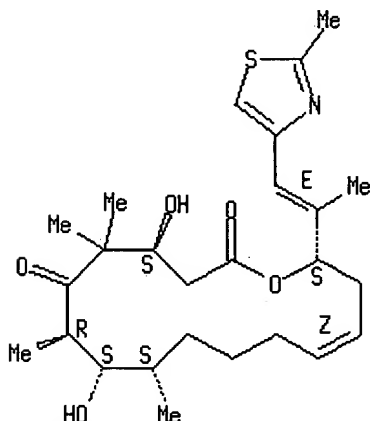
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(synthesis of epothilone B via a Suzuki coupling and insights into antitumor structure-activity relationships)

RN **186692-73-9** HCAPLUS

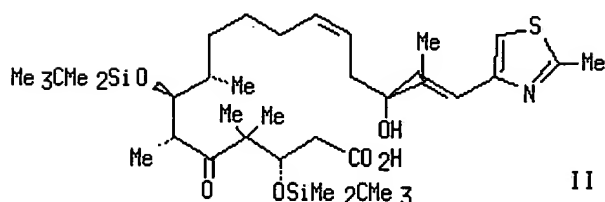
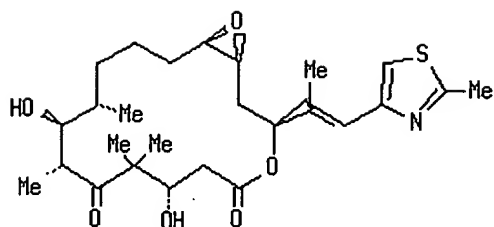
CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L12 ANSWER 30 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
<p>ACCESSION NUMBER: 1997:206419 HCAPLUS</p> <p>DOCUMENT NUMBER: 126:251010</p> <p>TITLE: Total synthesis of epothilone A: the macrolactonization approach</p> <p>AUTHOR(S): Nicolaou, K. C.; Sarabia, Francisco; Ninkovic, Sacha; Yang, Zhen</p> <p>CORPORATE SOURCE: Dep. Chem., Skaggs Inst. Chem. Biol. Scripps Res. Inst., La Jolla, CA, 92037, USA</p> <p>SOURCE: Angewandte Chemie, International Edition in English (1997), 36(5), 525-527</p> <p>PUBLISHER: VCH</p> <p>DOCUMENT TYPE: Journal</p> <p>LANGUAGE: English</p> <p>OTHER SOURCE(S): CASREACT 126:251010</p> <p>GI</p>	



AB Epothilone A (I) was prepd. via a highly convergent and flexible route with macrolactonization of hydroxy acid II as the key step.

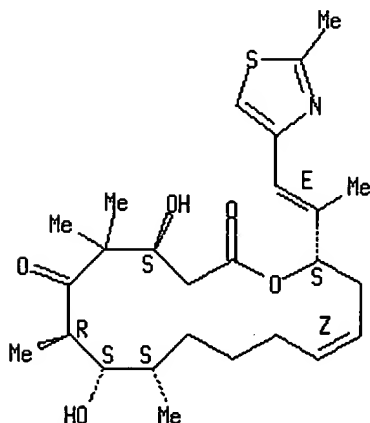
IT **186692-73-9P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(total synthesis of epothilone A via a macrolactonization approach)

RN **186692-73-9** HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.

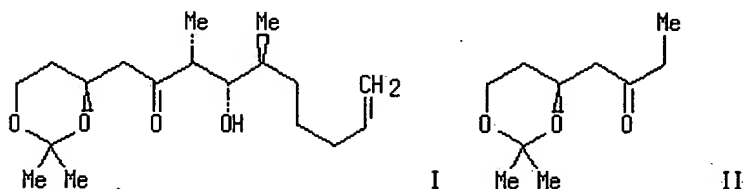


L12 ANSWER 31 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER:	1997:206418 HCAPLUS
DOCUMENT NUMBER:	126:277316
TITLE:	Total synthesis of (-)-epothilone A
AUTHOR(S):	Schinzer, Dieter; Limberg, Anja; Bauer, Armin; Boehm, Oliver M.; Cordes, Martin
CORPORATE SOURCE:	Dip. Chim., Inst. Org. Chem. Tech. Univ. Hagenring, Braunschweig, D-38106, Germany
SOURCE:	Angewandte Chemie, International Edition in English (1997), 36(5), 523-524

PUBLISHER: VCH
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 126:277316
GI



AB Stereoselective total synthesis of (-)-epothilone A and epothilone C was reported. The key step was the diastereoselective prepn. of intermediate ketone I by an aldol condensation of II with (S)-2-methyl-6-heptenal.

IT **186692-73-9P**, Epothilone C

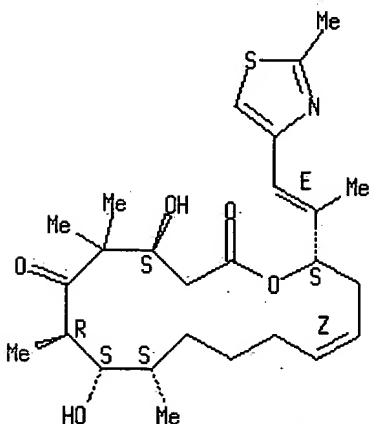
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(total synthesis of (-)-epothilone A)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L12 ANSWER 32 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER: 1997:175662 HCAPLUS

DOCUMENT NUMBER: 126:225133

TITLE: Remote Effects in Macrolide Formation through Ring-Forming Olefin Metathesis: An Application to the Synthesis of Fully Active Epothilone Congeners

AUTHOR(S): Meng, Dongfang; Su, Dai-Shi; Balog, Aaron; Bertinato, Peter; Sorensen, Erik J.; Danishefsky, Samuel J.; Zheng, Yu-Huang; Chou, Ting-Chao; He, Lifeng; Horwitz, Susan B.

CORPORATE SOURCE: Laboratories for Bioorganic Chemistry and Biochemical Pharmacology, Sloan-Kettering Institute for Cancer Research, New York, NY, 10021, USA

SOURCE: Journal of the American Chemical Society (1997),

119(11), 2733-2734
 CODEN: JACSAT; ISSN: 0002-7863
 PUBLISHER: American Chemical Society
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 OTHER SOURCE(S): CASREACT 126:225133
 GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB A ring closing olefin metathesis strategy for the synthesis of the previously encountered desoxyepothilone A (I) is described. A merging of the alkyl segment II (carbons 12-21) and acyl segment III (carbons 3-11) through an intermol. aldol-condensation reaction provided substrates needed for ring closing olefin metathesis. Thus, thiazole IV underwent olefin metathesis in C₆H₆ contg. 50 mol % (PhCH₃)[P(cyclohexyl)₃]₂RuCl₂ to give 65% II and its E-isomer (Z:E 1:2). The results of these cyclization indicate a remarkable sensitivity to permutations of functionality at centers remote from the site of olefin metathesis. The in vitro biol. activity of E and Z desoxyepothilone as well as several related congeners is also described. I has IC₅₀ range of 0.012-0.022 μ M against drug-sensitive and -resistant human leukemic CCRF-CEM cell lines.

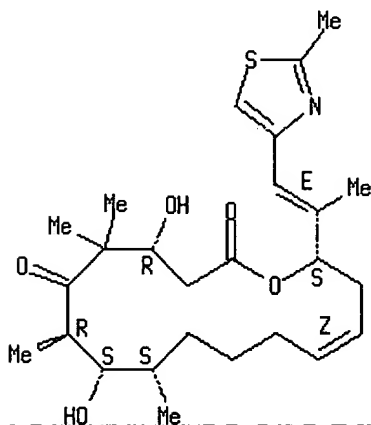
IT 188259-95-2P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
 (prepn. of antitumor epothilone congeners via ring-forming olefin metathesis)

RN 188259-95-2 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4R,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
 Double bond geometry as shown.



L12 ANSWER 33 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
--------------	----------------------

ACCESSION NUMBER: 1997:117381 HCAPLUS
 DOCUMENT NUMBER: 126:199371
 TITLE: Total synthesis of epothilone A: the olefin metathesis approach
 AUTHOR(S): Yang, Zhen; He, Yun; Vourloumis, Dionisios; Vallberg,

CORPORATE SOURCE: Hans; Nicolaou, K. C.
Department Chemistry Skaggs Institute Chemical
Biology, Scripps Research Institute, La Jolla, CA,
92037, USA

SOURCE: Angewandte Chemie, International Edition in English
(1997), 36(1/2), 166-168
CODEN: ACIEAY; ISSN: 0570-0833

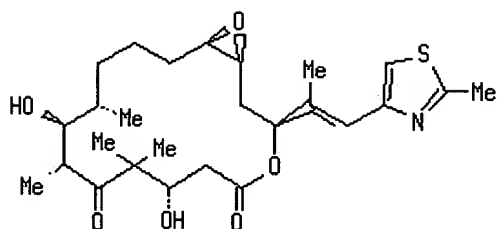
PUBLISHER: VCH

DOCUMENT TYPE: Journal

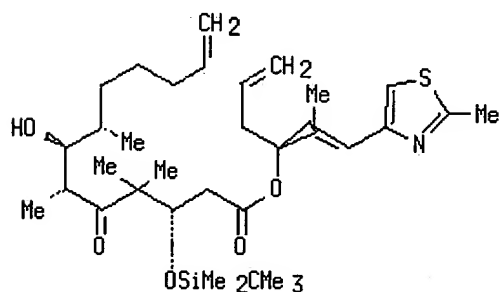
LANGUAGE: English

OTHER SOURCE(S): CASREACT 126:199371

GI



I



II

AB The asym. total synthesis of epothilone A (I) from EtCOCMe₂CHO, (S)-H₂C:CH(CH₂)₃CHMeCHO and Et 2-methylthiazole-4-carboxylate via metathesis of olefin II is described.

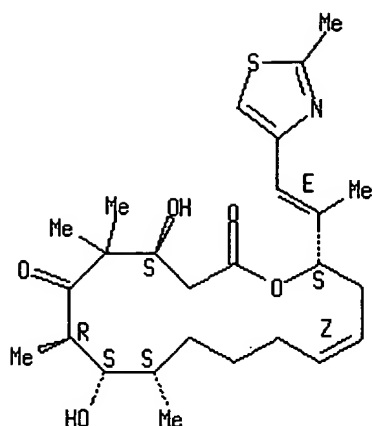
IT **186692-73-9P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(total synthesis of epothilone A via an olefin metathesis)

RN **186692-73-9** HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

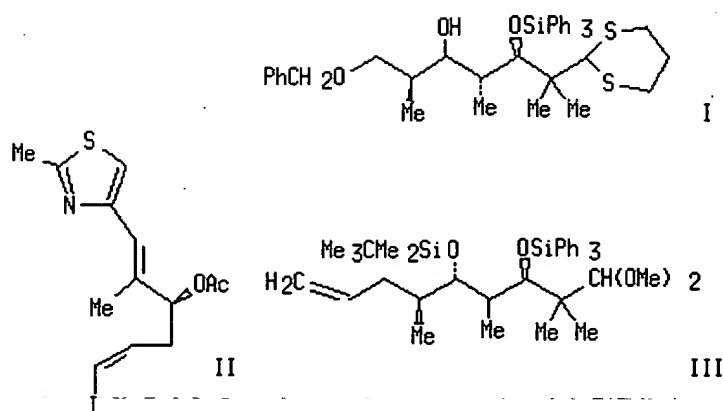
Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L12 ANSWER 34 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER: 1997:72321 HCAPLUS
 DOCUMENT NUMBER: 126:144023
 TITLE: Total synthesis of (-)-epothilone A
 AUTHOR(S): Balog, Aaron; Meng, Dongfang; Kamenecka, Ted; Bertinato, Peter; Su, Dai-Shi; Sorensen, Erik J.; Danishefsky, Samuel J.
 CORPORATE SOURCE: Lab. for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, New York, NY, 10021, USA
 SOURCE: Angewandte Chemie, International Edition in English (1997), Volume Date 1996, 35(23/24), 2801-2803
 CODEN: ACIEAY; ISSN: 0570-0833
 PUBLISHER: VCH
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 GI



AB (-)-Epothilone A was prepd. from dithiane I, (R)-glycidol and [(2-methyl-1,3-thiazol-4-yl)methyl]diphenylphosphine oxide via a B-alkyl Suzuki coupling of thiazole II with acetal III followed by closure of the macrocycle with an aldol reaction.

IT **186692-73-9P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

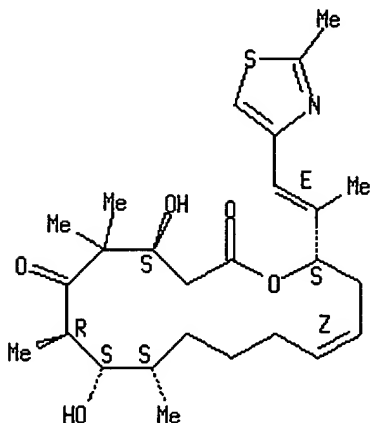
(total synthesis of (-)-epothilone A via a B-alkyl Suzuki coupling

followed by closure of the macrocycle with an aldol reaction)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-
[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-
(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



=> file caold

COST IN U.S. DOLLARS

SINCE FILE ENTRY	TOTAL SESSION
186.26	474.49

FULL ESTIMATED COST

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE ENTRY	TOTAL SESSION
-24.78	-24.78

CA SUBSCRIBER PRICE

FILE 'CAOLD' ENTERED AT 17:10:28 ON 22 AUG 2002

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FILE COVERS 1907-1966

FILE LAST UPDATED: 01 May 1997 (19970501/UP)

This file contains CAS Registry Numbers for easy and accurate substance identification. Title keywords, authors, patent assignees, and patent information, e.g., patent numbers, are now searchable from 1907-1966. TIFF images of CA abstracts printed between 1907-1966 are available in the PAGE display formats.

This file supports REGISTRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

=> d his

(FILE 'HOME' ENTERED AT 16:57:10 ON 22 AUG 2002)

FILE 'REGISTRY' ENTERED AT 16:57:18 ON 22 AUG 2002

L1 STRUCTURE UPLOADED

L2 11 S L1

L3 235 S L1 FULL

FILE 'HCAPLUS' ENTERED AT 17:02:57 ON 22 AUG 2002

L4 134 S L3

FILE 'REGISTRY' ENTERED AT 17:03:04 ON 22 AUG 2002

L5 STRUCTURE UPLOADED

L6 8 S L5

L7 121 S L5 FULL

FILE 'HCAPLUS' ENTERED AT 17:07:15 ON 22 AUG 2002

L8 132 S L7

L9 34 S L8 AND PD < SEPTEMBER 1998

L10 6 S L8 AND KLAR, U?/AU

L11 0 S L9 AND KLAR, U?/AU

L12 34 S L9 NOT L10

FILE 'CAOLD' ENTERED AT 17:10:28 ON 22 AUG 2002

=> s 17

L13 0 L7

=> log y

COST IN U.S. DOLLARS

SINCE FILE
ENTRY

TOTAL
SESSION

FULL ESTIMATED COST

0.38

474.87

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE
ENTRY

TOTAL
SESSION

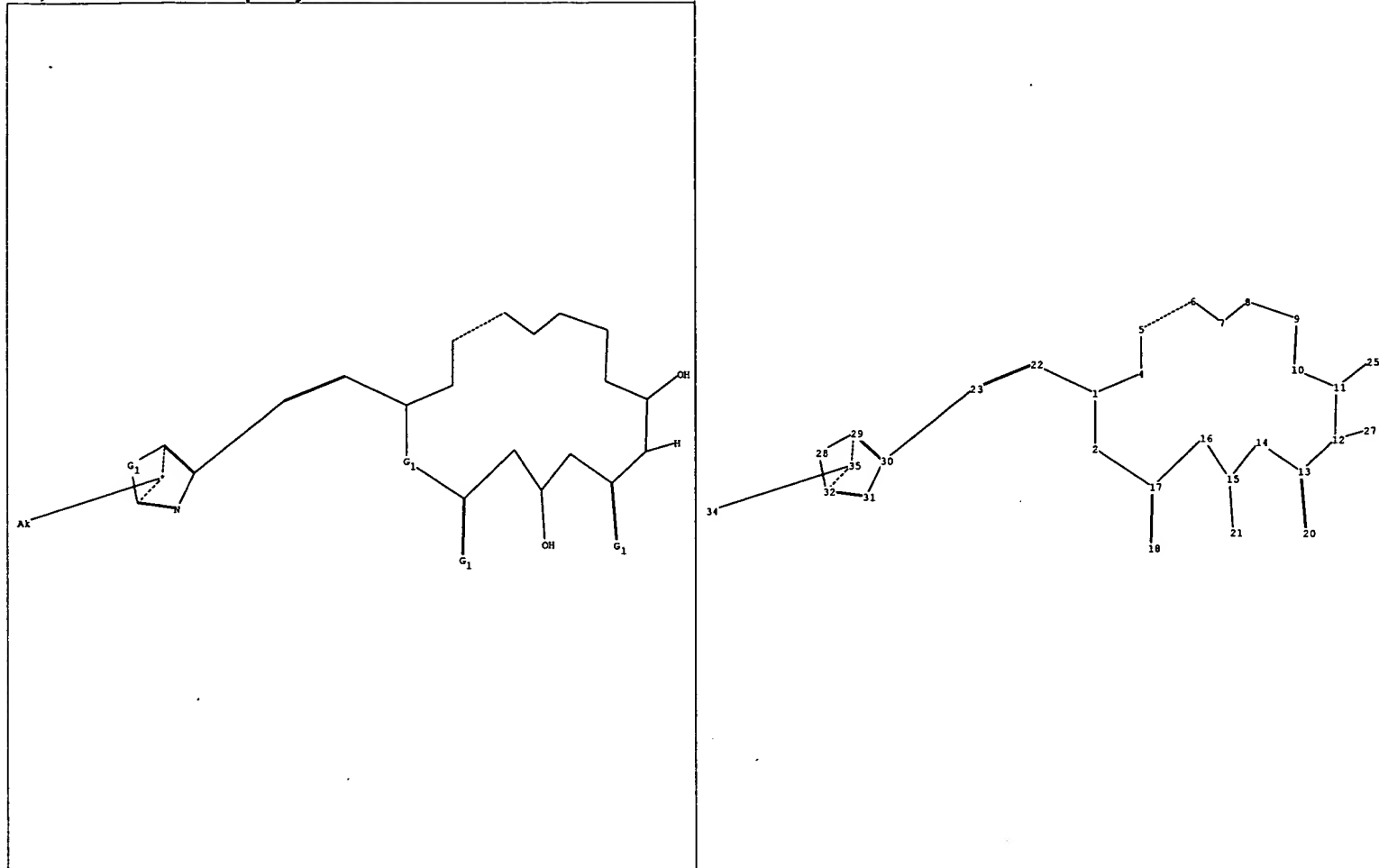
CA SUBSCRIBER PRICE

0.00

-24.78

STN INTERNATIONAL LOGOFF AT 17:10:52 ON 22 AUG 2002

STN Structure : query.str



chain nodes :

18 20 21 22 23 25 27 34

ring nodes :

1 2 4 5 6 7 8 9 10 11 12 13 14 15 16 17 28 29 30 31 32

chain bonds :

1-22 11-25 12-27 13-20 15-21 17-18 22-23 23-30

ring bonds :

1-2 1-4 2-17 4-5 5-6 6-7 7-8 8-9 9-10 10-11 11-12 12-13 13-14 14-15 15-16
16-17 28-29 28-32 29-30 30-31 31-32

exact/norm bonds :

1-2 1-4 1-22 2-17 4-5 5-6 6-7 7-8 8-9 9-10 10-11 11-12 11-25 12-13 12-27
13-14 13-20 14-15 15-16 15-21 16-17 17-18 22-23 23-30 28-29 28-32 29-30 30-31
31-32

isolated ring systems :

containing 1 : 28 :

G1:O,S

G2:CH3,Et

Match level :

1:Atom 2:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom 12:Atom
13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:Atom 20:Atom 21:CLASS 22:CLASS
23:CLASS 25:CLASS 27:CLASS 28:Atom 29:Atom 30:Atom 31:Atom 32:Atom 34:CLASS
35:CLASS

Session text above this point is available in the transcript,
available from the Transcript Assistant on the toolbar.

=> file reg

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

1.90

2.11

FILE 'REGISTRY' ENTERED AT 18:16:22 ON 22 AUG 2002

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STRUCTURE FILE UPDATES: 21 AUG 2002 HIGHEST RN 444646-89-3

DICTIONARY FILE UPDATES: 21 AUG 2002 HIGHEST RN 444646-89-3

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

Please note that search-term pricing does apply when
conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Calculated physical property data is now available. See HELP PROPERTIES
for more information. See STNote 27, Searching Properties in the CAS
Registry File, for complete details:

<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

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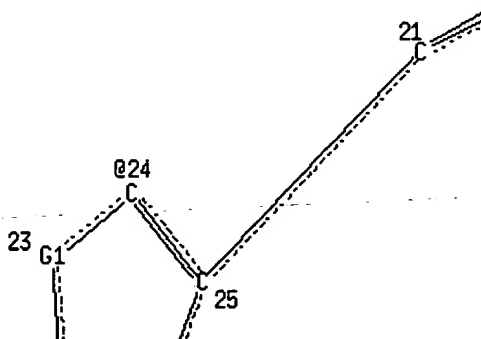
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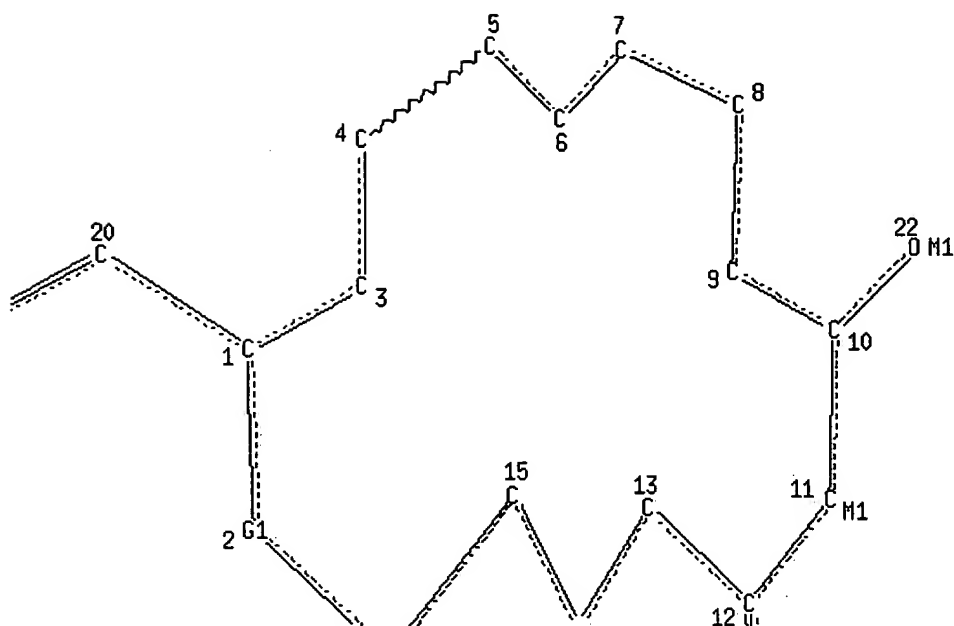
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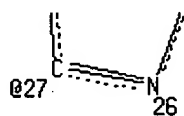
L2 STR

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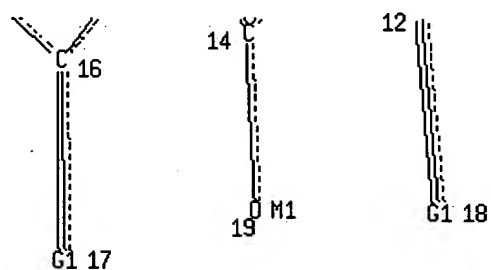


Page 1-B



AK 028

Page 2-A



Page 2-B

VAR G1=29/30

VPA 28-24/27 S

NODE ATTRIBUTES:

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HCOUNT	IS	M1	AT	19
HCOUNT	IS	M1	AT	22
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 DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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 NUMBER OF NODES IS 30

STEREO ATTRIBUTES: NONE

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 SAMPLE SCREEN SEARCH COMPLETED - 76 TO ITERATE

100.0% PROCESSED 76 ITERATIONS 18 ANSWERS
 SEARCH TIME: 00.00.02

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
 BATCH **COMPLETE**
 PROJECTED ITERATIONS: 997 TO 2043
 PROJECTED ANSWERS: 106 TO 614

L3 18 SEA SSS SAM L2

=> s 12 full
 THE ESTIMATED SEARCH COST FOR FILE 'REGISTRY' IS 139.90 U.S. DOLLARS
 DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
 FULL SEARCH INITIATED 18:17:10 FILE 'REGISTRY'
 FULL SCREEN SEARCH COMPLETED - 1426 TO ITERATE

100.0% PROCESSED 1426 ITERATIONS 292 ANSWERS
 SEARCH TIME: 00.00.03

L4 292 SEA SSS FUL L2

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COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	140.66	142.77

FILE 'HCAPLUS' ENTERED AT 18:17:16 ON 22 AUG 2002
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FILE COVERS 1907 - 22 Aug 2002 VOL 137 ISS 8
FILE LAST UPDATED: 21 Aug 2002 (20020821/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.

=> s 14

L5 143 L4

=> s 15 and pd < september 1998

18872712 PD < SEPTEMBER 1998

(PD<19980900)

L6 35 L5 AND PD < SEPTEMBER 1998

=> d 16, ibib abs fhitr, 1

L6 ANSWER 1 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER:	2000:316343 HCAPLUS
	Correction of: 1997:528752
DOCUMENT NUMBER:	132:293587
	Correction of: 127:149021
TITLE:	The Olefin Metathesis Approach to Epothilone A and Its Analogs
AUTHOR(S):	Nicolaou, K. C.; He, Y.; Vourloumis, D.; Vallberg, H.; Roschangar, F.; Sarabia, F.; Ninkovic, S.; Yang, Z.; Trujillo, J. I.
CORPORATE SOURCE:	Institute for Chemical Biology, La Jolla, CA, 92037, USA
SOURCE:	Journal of the American Chemical Society (1997), 119(34), 7960-7973
	CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER:	American Chemical Society
DOCUMENT TYPE:	Journal
LANGUAGE:	English
GI	

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The olefin metathesis approach to epothilone A (I) and several diastereomeric analogs is described. Key building blocks II, (S)-OHCH(Me)CH₂CH₂CH=CH₂, and (S)-MeCH₂COC(Me)CH(OSiMe₂CMe₃)CH₂CO₂H were constructed in optically active form and were coupled and elaborated to olefin metathesis precursor III (R = SiMe₂CMe₃) via an aldol reaction and an esterification coupling. Olefin metathesis of compd. III (R = SiMe₂CMe₃), under the catalytic influence of RuCl₂(:CHPh)(PCy₃)₂, furnished cis- and trans-cyclic olefins IV (R = SiMe₂CMe₃). Epoxidn. of (Z)-IV (R = H) gave I and several analogs, whereas epoxidn. of (E)-IV (R = H) resulted in addnl. epothilones. Similar elaboration of isomeric as well as simpler intermediates resulted in yet another series of epothilone analogs and model systems.

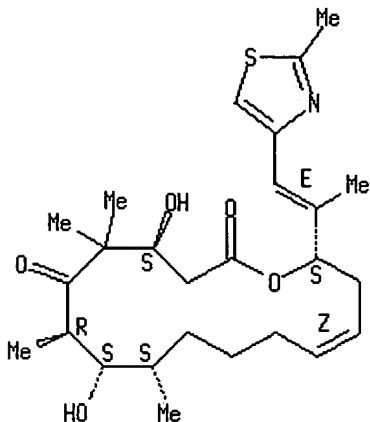
IT 186692-73-9P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of epothilone A and analogs via olefin metathesis)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



=> d his

(FILE 'HOME' ENTERED AT 18:12:21 ON 22 AUG 2002)

FILE 'REGISTRY' ENTERED AT 18:12:27 ON 22 AUG 2002
L1 STRUCTURE UPLOADED

FILE 'REGISTRY' ENTERED AT 18:16:22 ON 22 AUG 2002
L2 STRUCTURE UPLOADED

L3 18 S L2

L4 292 S L2 FULL

FILE 'HCAPLUS' ENTERED AT 18:17:16 ON 22 AUG 2002

L5 143 S L4

L6 35 S L5 AND PD < SEPTEMBER 1998

=> d 16, ibib abs fhitr, 1-35

L6 ANSWER 1 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER:	2000:316343 HCAPLUS
	Correction of: 1997:528752
DOCUMENT NUMBER:	132:293587
	Correction of: 127:149021
TITLE:--	The Olefin-Metathesis Approach to Epothilone A and Its Analogs
AUTHOR(S):	Nicolaou, K. C.; He, Y.; Vourloumis, D.; Vallberg, H.; Roschangar, F.; Sarabia, F.; Ninkovic, S.; Yang, Z.; Trujillo, J. I.
CORPORATE SOURCE:	Institute for Chemical Biology, La Jolla, CA, 92037, USA
SOURCE:	Journal of the American Chemical Society (1997), 119(34), 7960-7973
	CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER:	American Chemical Society

DOCUMENT TYPE: Journal
 LANGUAGE: English
 GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The olefin metathesis approach to epothilone A (I) and several diastereomeric analogs is described. Key building blocks II, (S)-OHCCH(Me)CH₂CH₂CH=CH₂, and (S)-MeCH₂COC(Me)CH(OSiMe₂CMe₃)CH₂CO₂H were constructed in optically active form and were coupled and elaborated to olefin metathesis precursor III (R = SiMe₂CMe₃) via an aldol reaction and an esterification coupling. Olefin metathesis of compd. III (R = SiMe₂CMe₃), under the catalytic influence of RuCl₂(:CHPh)(PCy₃)₂, furnished cis- and trans-cyclic olefins IV (R = SiMe₂CMe₃). Epoxidn. of (Z)-IV (R = H) gave I and several analogs, whereas epoxidn. of (E)-IV (R = H) resulted in addnl. epothilones. Similar elaboration of isomeric as well as simpler intermediates resulted in yet another series of epothilone analogs and model systems.

IT 186692-73-9P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

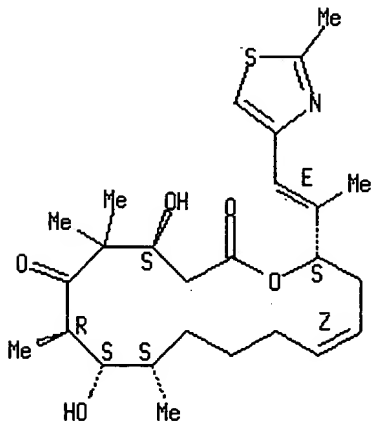
(synthesis of epothilone A and analogs via olefin metathesis)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

Double bond geometry as shown.



L6 ANSWER 2 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
-----------	-------------------

ACCESSION NUMBER: 1999:19340 HCAPLUS

DOCUMENT NUMBER: 130:217758

TITLE: Desoxyepothilone B is curative against human tumor xenografts that are refractory to paclitaxel

AUTHOR(S): Chou, Ting-Chao; Zhang, Xiu-Guo; Harris, Christina R.; Kuduk, Scott D.; Balog, Aaron; Savin, Kenneth A.; Bertino, Joseph R.; Danishefsky, Samuel J.

CORPORATE SOURCE: Molecular Pharmacology and Therapeutics Program, Sloan-Kettering Institute for Cancer Research, New York, NY, 10021, USA

SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1998), 95(26), 15798-15802

PUBLISHER: CODEN: PNASA6; ISSN: 0027-8424
 DOCUMENT TYPE: National Academy of Sciences
 LANGUAGE: Journal
 English

AB The epothilones are naturally occurring, cytotoxic macrolides that function through a paclitaxel (Taxol)-like mechanism. Although structurally dissimilar, both classes of mols. lead to the arrest of cell division and eventual cell death by stabilizing cellular microtubule assemblies. The epothilones differ in their ability to retain activity against multidrug-resistant (MDR) cell lines and tumors where paclitaxel fails. In the current account, we focus on the relationship between epothilone and paclitaxel in the context of tumors with multiple drug resistance. The epothilone analog Z-12,13-desoxyepothilone B (dEpoB) is >35,000-fold more potent than paclitaxel in inhibiting cell growth in the MDR DC-3F/ADX cell line. Various formulations, routes, and schedules of i.v. administration of dEpoB have been tested in nude mice. Slow infusion with a Cremophor-ethanol vehicle proved to be the most beneficial in increasing efficacy and decreasing toxicity. Although dEpoB performed similarly to paclitaxel in sensitive tumors xenografts (MX-1 human mammary and HT-29 colon tumor), its effects were clearly superior against MDR tumors. When dEpoB was administered to nude mice bearing our MDR human lymphoblastic T cell leukemia (CCRF-CEM/paclitaxel), dEpoB demonstrated a full curative effect. For human mammary adenocarcinoma MCF-7/Adr cells refractory to paclitaxel, dEpoB reduced the established tumors, markedly suppressed tumor growth, and surpassed other commonly used chemotherapy drugs such as adriamycin, vinblastine, and etoposide in beneficial effects.

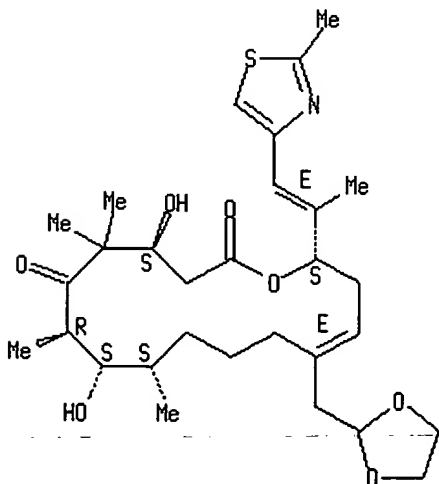
IT 198475-07-9

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
 (antitumor activity of desoxyepothilone B analogs)

RN 198475-07-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 13-[(1,3-dioxolan-2-ylmethyl)-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13E,16S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
 Double bond geometry as shown.



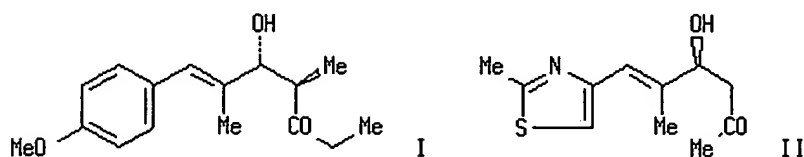
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 3 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER: 1998:805542 HCAPLUS

DOCUMENT NUMBER: 130:153488
 TITLE: The antibody catalysis route to the total synthesis of epothilones
 AUTHOR(S): Sinha, Subhash C.; Barbas, Carlos F., III; Lerner, Richard A.
 CORPORATE SOURCE: The Skaggs Institute for Chemical Biology and the Department of Molecular Biology, The Scripps Research Institute, La Jolla, CA, 92037, USA
 SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1998), 95(25), 14603-14608
 CODEN: PNASA6; ISSN: 0027-8424
 PUBLISHER: National Academy of Sciences
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 OTHER SOURCE(S): CASREACT 130:153488
 GI



AB A total synthesis of epothilones A and C via antibody-catalyzed aldol and retro-aldol reactions was described. Epothilone precursors (+)-I and (-)-II were prep'd. using aldolase antibody 38C2 as a catalyst. These precursors were then converted to epothilones A and C to complete the total synthesis.

IT **186692-73-9P**, Epothilone C

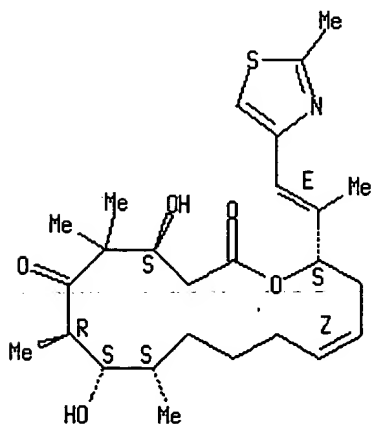
RL: BPN (Biosynthetic preparation); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)

(total synthesis of epothilones via antibody 38C2 catalyzed retro-aldol reactions)

RN **186692-73-9** HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
 Double bond geometry as shown.



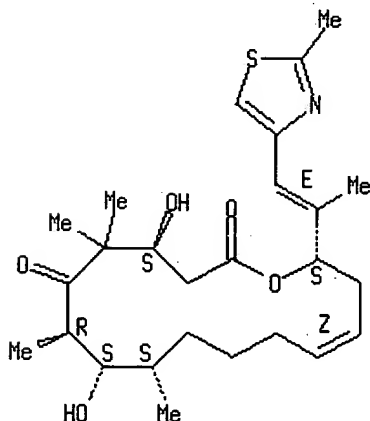
REFERENCE COUNT: 62 THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 4 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER: 1998:760826 HCAPLUS
 DOCUMENT NUMBER: 130:95407
 TITLE: Derivatization of the C12-C13 functional groups of
 epothilones A, B and C
 AUTHOR(S): Sefkow, Michael; Kiffe, Michael; Hofle, Gerhard
 CORPORATE SOURCE: Gesellschaft fur Biotechnologische Forschung mbH, Abt.
 Naturstoffchemie, Braunschweig, D-38124, Germany
 SOURCE: Bioorganic & Medicinal Chemistry Letters (1998),
 8(21), 3031-3036
 CODEN: BMCLE8; ISSN: 0960-894X
 PUBLISHER: Elsevier Science Ltd.
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 OTHER SOURCE(S): CASREACT 130:95407
 AB Epothilone A reacted with hydrohalic acids to give C12-C13 halohydrin
 regioisomers (ratios: 2:1 - 4:1), whereas epothilone B gave under the same
 conditions the isomerically pure C12 halo C13 hydroxy deriv. With
 non-nucleophilic Bronstedt acids and with Lewis acids a highly solvent
 dependent product distribution and some unexpected rearrangement products
 were obsd. Epothilone C bearing a double bond between C12 and C13 was
 regioselectively dihydroxylated or hydrogenated at that position.
 IT **186692-73-9**, Epothilone C
 RL: RCT (Reactant); RACT (Reactant or reagent)
 (derivatization of the C12-C13 functional groups of epothilones A, B
 and C)
 RN **186692-73-9** HCAPLUS
 CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-
 [(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-
 (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
 Double bond geometry as shown.



REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

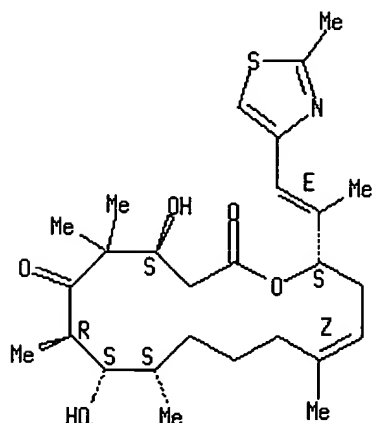
L6 -- ANSWER 5 OF 35 -- HCAPLUS -- COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER: 1998:732784 HCAPLUS
 DOCUMENT NUMBER: 130:81320
 TITLE: Easy access to the epothilone family - synthesis of
 epothilone B
 AUTHOR(S): Mulzer, Johann; Mantoulidis, Andreas; Ohler, Elisabeth
 CORPORATE SOURCE: Inst. fur Organische Chemie, Univ. Wien, Vienna,
 A-1090, Austria

SOURCE: Tetrahedron Letters (1998), 39(47), 8633-8636
 CODEN: TELEAY; ISSN: 0040-4039
 PUBLISHER: Elsevier Science Ltd.
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 OTHER SOURCE(S): CASREACT 130:81320
 AB An easy access to four out of five naturally occurring epothilones (A-E) is reported. Key steps are an enantioselective Mukaiyama type aldol reaction, (E)- and (Z)-selective olefinations, and a sulfone alkylation.
 IT **189453-10-9P**, Epothilone D
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (synthesis of epothilone B)
 RN 189453-10-9 HCAPLUS
 CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
 Double bond geometry as shown.

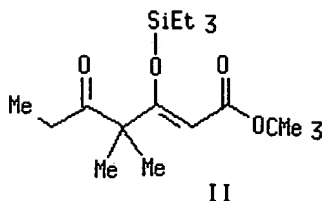
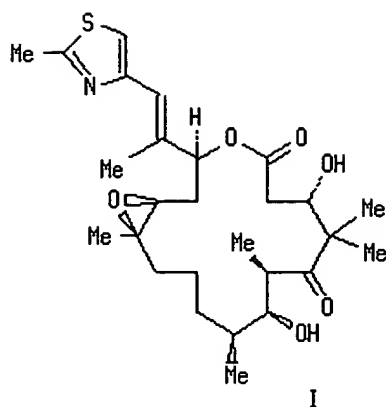


REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 6 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER:	1998:726876 HCAPLUS
DOCUMENT NUMBER:	130:81319
TITLE:	A novel aldol condensation with 2-methyl-4-pentenal and its application to an improved total synthesis of epothilone B
AUTHOR(S):	Balog, Aaron; Harris, Christina; Savin, Kenneth; Zhang, Xiu-Guo; Chou, Ting Chao; Danishefsky, Samuel J.
CORPORATE SOURCE:	Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, New York, NY, 10021, USA
SOURCE:	Angewandte Chemie, International Edition (1998), 37(19), 2675-2678 CODEN: ACIEF5; ISSN: 1433-7851
PUBLISHER:	Wiley-VCH Verlag GmbH
DOCUMENT TYPE:	Journal
LANGUAGE:	English
OTHER SOURCE(S):	CASREACT 130:81319
GI	



AB Epothilone B was prepd. in 9 steps via aldol condensation of (S)-2-methyl-4-pentenal with the enolate I.

IT **189453-10-9P**

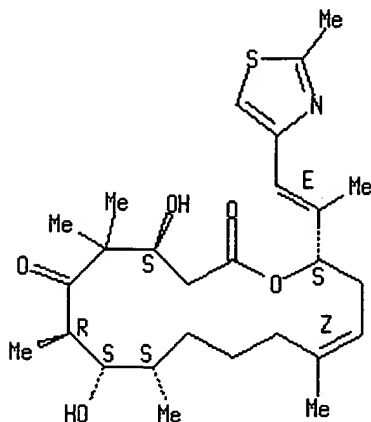
RL: SPN (Synthetic preparation); PREP (Preparation)

(novel aldol condensation with 2-methyl-4-pentenal and application to improved total synthesis of epothilone B)

RN 189453-10-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



REFERENCE COUNT:

52

THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 7 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER:

1998:534644 HCAPLUS

DOCUMENT NUMBER:

129:239597

TITLE:

Desoxyepothilone B: an efficacious microtubule-targeted antitumor agent with a promising in vivo profile relative to epothilone B

AUTHOR(S):

Chou, Ting-Chao; Zhang, Xiu-Guo; Balog, Aaron; Su, Dai-Shi; Meng, Dongfang; Savin, Kenneth; Bertino, Joseph R.; Danishefsky, Samuel J.

CORPORATE SOURCE:

Molecular Pharmacology and Therapeutics Program, Cornell University Graduate School of Medical Sciences, New York, NY, 10021, USA

SOURCE:

Proceedings of the National Academy of Sciences of the United States of America (1998), 95(16), 9642-9647

CODEN: PNASA6; ISSN: 0027-8424

PUBLISHER: National Academy of Sciences

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A new class of 16-membered macrolides, the epothilones (Epos), has been synthesized and evaluated for antitumor potential in vitro and in vivo. Recent studies in these and other labs. showed that epothilones and paclitaxel (paclitaxel) share similar mechanisms of action in stabilizing microtubule arrays as indicated by binding-displacement studies, substitution for paclitaxel in paclitaxel-dependent cell growth, and electron microscopic exams. The present study examd. cell growth-inhibitory effects in two rodent and three human tumor cell lines and their drug-resistant sublines. Although paclitaxel showed as much as 1,970-fold cross-resistance to the sublines resistant to paclitaxel, adriamycin, vinblastine, or actinomycin D, most epothilones exhibit little or no cross-resistance. In multidrug-resistant CCRF-CEM/VBL100 cells, IC50 values for EpoA (1), EpoB (2), desoxyEpoA (3) (dEpoA), desoxyEpoB (4) (dEpoB), and paclitaxel were 0.02, 0.002, 0.012, 0.017, and 4.14 μ M, resp. In vivo studies, using i.p. administration, indicated that the parent, EpoB, was highly toxic to mice and showed little therapeutic effect when compared with a lead compd., dEpoB. More significantly, dEpoB (25-40 mg/kg, Q2Dx5, i.p.) showed far superior therapeutic effects and lower toxicity than paclitaxel, doxorubicin, camptothecin, or vinblastine (at maximal tolerated doses) in parallel expts. For mammary adenocarcinoma xenografts resistant to adriamycin, MCF-7/Adr, superior therapeutic effects were obtained with dEpoB compared with paclitaxel when i.p. regimens were used. For ovarian adenocarcinoma xenografts, SK-OV-3, dEpoB (i.p.), and paclitaxel (i.v.) gave similar therapeutic effects. In nude mice bearing a human mammary carcinoma xenograft (MX-1), marked tumor regression and cures were obtained with dEpoB.

IT 189453-10-9, Desoxyepothilone B

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

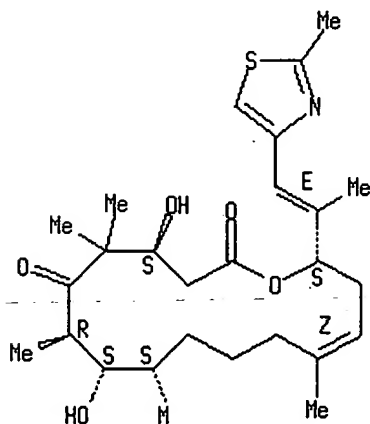
(desoxyepothilone B is an efficacious microtubule-targeted antitumor agent with a promising in vivo profile relative to epothilone B)

RN 189453-10-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

Double bond geometry as shown.

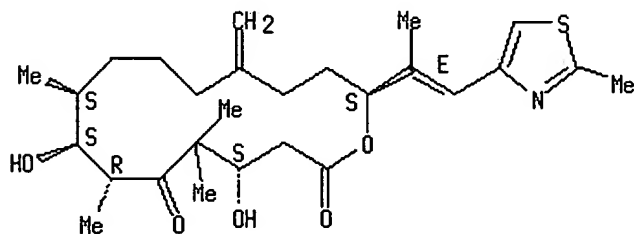


L6 ANSWER 8 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER: 1998:503765 HCAPLUS
 DOCUMENT NUMBER: 129:244965
 TITLE: Synthesis and biological properties of
 C12,13-cyclopropyl-epothilone A and related
 epothilones
 AUTHOR(S): Nicolaou, K. C.; Finlay, M. Ray V.; Ninkovic, Sacha;
 King, N. Paul; He, Yun; Li, Tianhu; Sarabia,
 Francisco; Vourloumis, Dionisios
 CORPORATE SOURCE: Dep. Chemistry, The Skaggs Inst. Chem. Biol., The
 Scripps Res. Inst., La Jolla, CA, 92037, USA
 SOURCE: Chemistry & Biology (1998), 5(7), 365-372
 CODEN: CBOLE2; ISSN: 1074-5521
 PUBLISHER: Current Biology Ltd.
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 OTHER SOURCE(S): CASREACT 129:244965
 AB Background: The epothilones are natural substances that are potently
 cytotoxic, having an almost identical mode of action to Taxol as
 tubulin-polymn. and microtubule-stabilizing agents. The development of
 detailed structure-activity relationships for these compds. and the
 further elucidation of their mechanism of action is of high priority.
 Results: The chem. synthesis of the C12,13-cyclopropyl analog of
 epothilone A and its C12,13-trans-diastereoisomer has been accomplished.
 These compds. and several other epothilone analogs have been screened for
 their ability to induce tubulin polymn. and death of a no. of tumor cells.
 Several interesting structure-activity trends within this family of
 compds. were identified. Conclusions: The results of the biol. tests
 conducted in this study have demonstrated that, although a no. of
 positions on the epothilone skeleton are amenable to modification without
 significant loss of biol. activity, the replacement of the epoxide moiety
 of epothilone A with a cyclopropyl group leads to total loss of activity.
 IT **213312-66-4**
 RL: RCT (Reactant); RACT (Reactant or reagent)
 (synthesis and biol. properties of C12,13-cyclopropyl-epothilone A and
 related epothilones)
 RN 213312-66-4 HCAPLUS
 CN Oxacyclohexadecane-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-13-
 methylene-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-,
 (4S,7R,8S,9S,16S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
 Double bond geometry as shown.

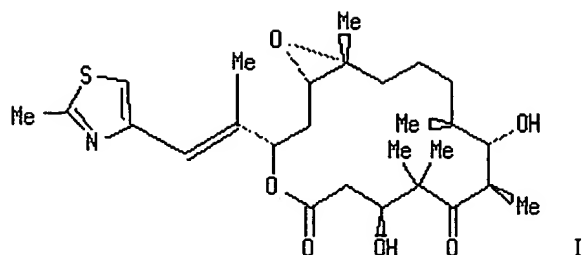


L6 ANSWER 9 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER: 1998:492150 HCAPLUS
 DOCUMENT NUMBER: 129:216449
 TITLE: Total synthesis of (-)-epothilone B
 AUTHOR(S): May, Scott A.; Grieco, Paul A.
 CORPORATE SOURCE: Department of Chemistry and Biochemistry, Montana
 State University, Bozeman, MT, 59717, USA
 SOURCE: Chemical Communications (Cambridge) (1998), (15),
 1597-1598

PUBLISHER: CODEN: CHCOFS; ISSN: 1359-7345
DOCUMENT TYPE: Royal Society of Chemistry
LANGUAGE: Journal
English
GI



AB The sixteen-membered ring macrolide (-)-epothilone B (I) has been synthesized by a route which features stereospecific methylation of an (E)- γ,δ -epoxy acrylate, the use of a double asym. reaction employing (R,R)-diisopropyltartrate and (E)-crotylboronate, ring closure by means of an olefin metathesis reaction.

IT 189453-10-9P

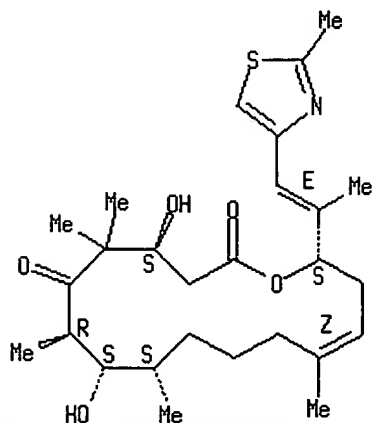
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(total synthesis of (-)-epothilone B)

RN 189453-10-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L6 ANSWER 10 OF 35 HCAPLUS COPYRIGHT 2002 ACS

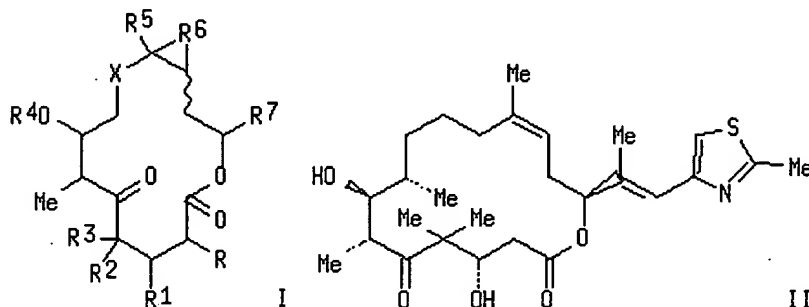
Full Text	Citing References
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ACCESSION NUMBER:	1998:405952 HCAPLUS
DOCUMENT NUMBER:	129:81625
TITLE:	Preparation of epothilone analogs as anticancer agents
INVENTOR(S):	Nicolaou, Costa Kyriacos; He, Yun; Ninkovic, Sacha; Pastor, Joaquin; Roschangar, Frank; Sarabia, Francisco; Vallberg, Hans; Vourloumis, Dionisios; Winssinger, Nicolas; Yang, Zhen; King, Nigel Paul; et al.
PATENT ASSIGNEE(S):	Novartis A.-G., Switz.; Scripps Research Institute
SOURCE:	PCT Int. Appl., 213 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
<u>WO 9825929</u>	<u>A1</u>	<u>19980618</u>	<u>WO 1997-EP7011</u>	<u>19971212</u>
W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG			
<u>AU 9857577</u>	<u>A1</u>	<u>19980703</u>	<u>AU 1998-57577</u>	<u>19971212</u>
<u>AU 746597</u>	B2	20020502		
<u>EP 944634</u>	<u>A1</u>	<u>19990929</u>	<u>EP 1997-953808</u>	<u>19971212</u>
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO			
<u>BR 9714140</u>	A	20000229	<u>BR 1997-14140</u>	<u>19971212</u>
<u>CN 1246862</u>	A	20000308	<u>CN 1997-181771</u>	<u>19971212</u>
<u>JP 2001504856</u>	T2	20010410	<u>JP 1998-526247</u>	<u>19971212</u>
PRIORITY APPLN. INFO.:			<u>US 1996-32864P</u>	P 19961213
			<u>US 1997-856533</u>	A 19970514
			<u>US 1997-923869</u>	A2 19970904
			<u>WO 1997-EP7011</u>	W 19971212

OTHER SOURCE(S): MARPAT 129:81625
GI



AB Epothilone A, epothilone B, analogs of epothilone and libraries of epothilone analogs of formula I [X = (CH₂)_n; n = 1-5; R₁ = OH, OMe, absent; R₂, R₃ = H, CH₂, Me; R₄ = H, Me, protecting group; R₅ = H, Me, CHO, (substituted) CO₂H, etc.; R₆ = O, CH₂, absent; R₇ = thiazolealkyl, etc.] are synthesized. Epothilone A and B are known anticancer agents that derive their anticancer activity by the prevention of mitosis through the induction and stabilization of microtubulin assembly. Several of the analogs are demonstrated to have a superior cytotoxic activity as compared to epothilone A or epothilone B as demonstrated by their enhanced ability to induce the polymn. and stabilization of microtubules. Thus, II was prepd. and was shown to induce tubulin polymn. at 94% relative to GTP, and inhibit carcinoma cell growth.

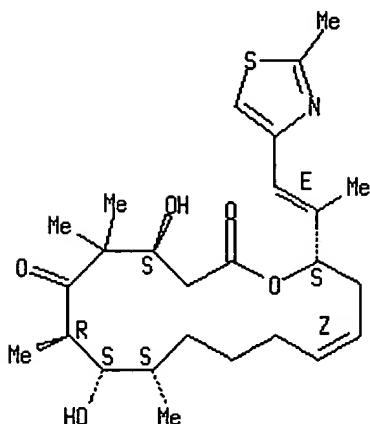
IT 186692-73-9P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of epothilone analogs as anticancer agents)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-
[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-
(9CI) (CA INDEX NAME)

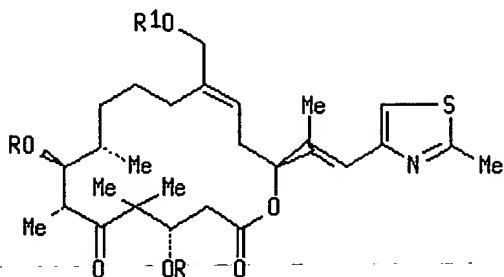
Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L6 ANSWER 11 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER: 1998:378435 HCAPLUS
DOCUMENT NUMBER: 129:189151
TITLE: Total synthesis of 26-hydroxy-epothilone B and related
analogues via a macrolactonization based strategy
AUTHOR(S): Nicolaou, K. C.; Finlay, M. Ray V.; Ninkovic, Sacha;
Sarabia, Francisco
CORPORATE SOURCE: Department of Chemistry and The Skaggs Institute for
Chemical Biology, The Scripps Research Institute, La
Jolla, CA, 92037, USA
SOURCE: Tetrahedron (1998), 54(25), 7127-7166
CODEN: TETRAB; ISSN: 0040-4020
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 129:189151
GI



AB The chem. synthesis of a series of 26-substituted epothilones B was
described. Fully protected 26-hydroxydesoxy-epothilone B I (R =
SiMe₂CMe₃, R1 = CPh₃), prepd. via a macrolactonization strategy, served as
a common precursor to the designed epothilones described. The synthesized
comps. were members of a large epothilone library of a no. of antitumor
agents.

IT 198475-04-6P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT

(Reactant or reagent)

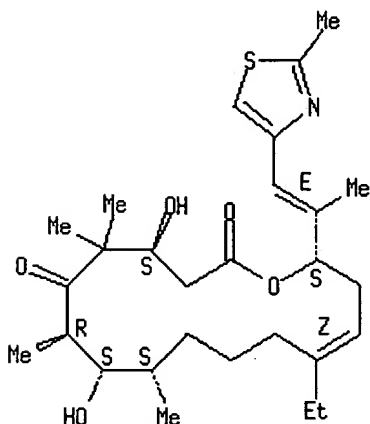
(total synthesis of 26-hydroxy-epothilone B and related analogs via a macrolactonization based strategy)

RN 198475-04-6 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 13-ethyl-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

Double bond geometry as shown.



L6 ANSWER 12 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Citing
Text References

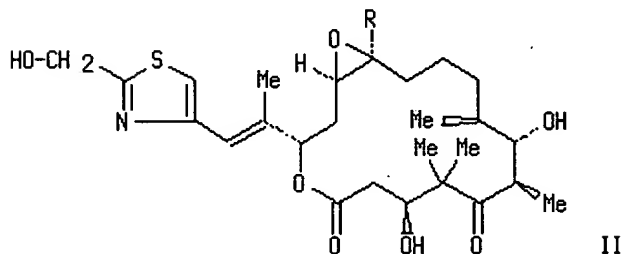
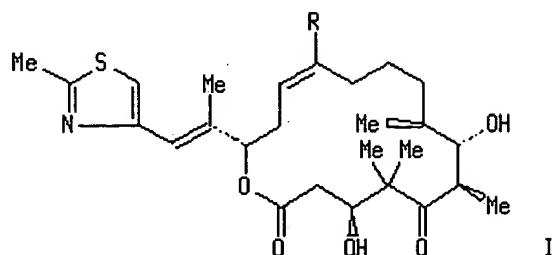
ACCESSION NUMBER: 1998:352834 HCAPLUS
DOCUMENT NUMBER: 129:53436
TITLE: Epothilone C, D, E and F, production process, and their use as cytostatics well as phytosanitary agents
INVENTOR(S): Reichenbach, Hans; Hofle, Gerhard; Gerth, Klaus; Steinmetz, Heinrich
PATENT ASSIGNEE(S): Gesellschaft Fur Biotechnologische Forschung m.b.H. (GBF), Germany; Reichenbach, Hans; Hofle, Gerhard; Gerth, Klaus; Steinmetz, Heinrich
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
<u>WO 9822461</u>	<u>A1</u>	<u>19980528</u>	<u>WO 1997-EP6442</u>	<u>19971118</u>
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
<u>AU 9854837</u>	<u>A1</u>	<u>19980610</u>	<u>AU 1998-54837</u>	<u>19971118</u>
<u>ZA 9710384</u>	<u>A</u>	<u>19990518</u>	<u>ZA 1997-10384</u>	<u>19971118</u>
<u>EP 941227</u>	<u>A1</u>	<u>19990915</u>	<u>EP 1997-951233</u>	<u>19971118</u>
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
<u>CN 1237970</u>	<u>A</u>	<u>19991208</u>	<u>CN 1997-199814</u>	<u>19971118</u>
<u>BR 9713363</u>	<u>A</u>	<u>20000125</u>	<u>BR 1997-13363</u>	<u>19971118</u>

JP 2001504474 T2 20010403
 TW 408119 B 20001011
 NO 9902338 A 19990514
 KR 2000053308 A 20000825
 PRIORITY APPLN. INFO.:

JP 1998-523208 19971118
 TW 1997-86117334 19980121
 NO 1999-2338 19990514
 KR 1999-704302 19990514
 DE 1996-19647580 A 19961118
 DE 1997-19707506 A 19970225
 WO 1997-EP6442 W 19971118

GI



AB The present invention concerns the epothilones, esp. epothilone C [I; R = H] and epothilone D [I; R = Me] as well as epothilone E [II; R = H] and epothilone F [II; R = Me], the prodn. process, and their application for producing therapeutic agents, including cytostatic agents as well as phytosanitary agents.

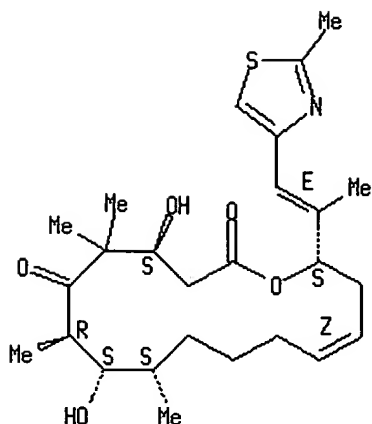
IT **186692-73-9P**, Epothilone C

RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
 (epothilone C, D, E and F, prodn. process, and use as cytostatics well as phytosanitary agents)

RN **186692-73-9** HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
 Double bond geometry as shown.



L6 ANSWER 13 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER: 1998:163596 HCAPLUS
DOCUMENT NUMBER: 128:217229
TITLE: Method for producing epothilones and the intermediate products obtained during the production process
INVENTOR(S): Schinzer, Dieter; Limberg, Anja; Bohm, Oliver M.; Bauer, Armin; Cordes, Martin
PATENT ASSIGNEE(S): Novartis Aktiengesellschaft, Switz.; Schinzer, Dieter; Limberg, Anja; Bohm, Oliver M.; Bauer, Armin; Cordes, Martin
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
<u>WO 9808849</u>	<u>A1</u>	<u>19980305</u>	<u>WO 1997-DE111</u>	<u>19970115</u>
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
<u>DE 19636343</u>	<u>C1</u>	<u>19971023</u>	<u>DE 1996-19636343</u>	<u>19960830</u>
<u>DE 19645361</u>	<u>A1</u>	<u>19980430</u>	<u>DE 1996-19645361</u>	<u>19961028</u>
<u>DE 19645362</u>	<u>A1</u>	<u>19980430</u>	<u>DE 1996-19645362</u>	<u>19961028</u>
<u>AU 9721493</u>	<u>A1</u>	<u>19980319</u>	<u>AU 1997-21493</u>	<u>19970115</u>
<u>AU 716610</u>	<u>B2</u>	<u>20000302</u>		
<u>EP 923583</u>	<u>A1</u>	<u>19990623</u>	<u>EP 1997-914077</u>	<u>19970115</u>
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
<u>JP 2001500851</u>	<u>T2</u>	<u>20010123</u>	<u>JP 1998-511141</u>	<u>19970115</u>
PRIORITY APPLN. INFO.:				
			<u>DE 1996-19636343</u>	<u>A</u> <u>19960830</u>
			<u>DE 1996-19645361</u>	<u>A</u> <u>19961028</u>
			<u>DE 1996-19645362</u>	<u>A</u> <u>19961028</u>
			<u>WO 1997-DE111</u>	<u>W</u> <u>19970115</u>

OTHER SOURCE(S): CASREACT 128:217229; MARPAT 128:217229
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB A method for producing epothilones I [R = H (A), Me (B)] is characterized by reaction of thiazole II with carboxylic acid III (B = CH₂Ph, THP, silyl protecting group; R = H, Me), followed by olefin metathesis in the presence of a noble metal catalyst, hydroxyl deprotection and epoxidn. Thus, epothilone A (I; R = H) was prepd. via acylation of II with III (R = H, B = SiMe₂CMe₃) in CH₂Cl₂ contg. DCC and DMAP, followed by olefin metathesis in CH₂Cl₂ contg. catalytic benzylidenebis(tricyclohexylphosphine) ruthenium dichloride, desilylation with aq. HF in Et₂O/MeCN and epoxidn. with dimethyldioxirane in acetone. Epothilones A and B are natural substances which are produced by microorganisms and have similar properties to those of taxol and, therefore, are of interest to the pharmaceutical chem.

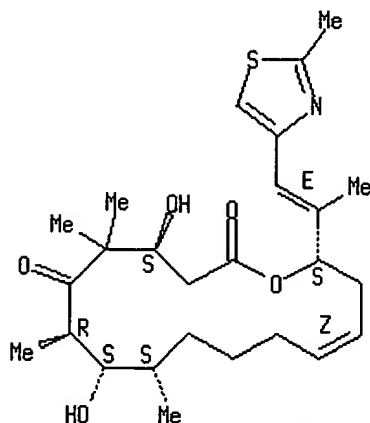
IT **186692-73-9P**, Epothilone C

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of epothilones via olefin metathesis)

RN **186692-73-9** HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

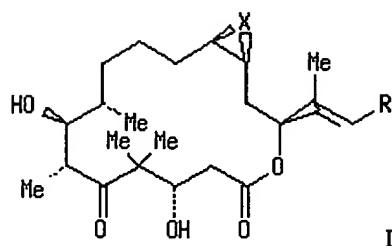
Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L6 ANSWER 14 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER:	1998:150476 HCAPLUS
DOCUMENT NUMBER:	128:230166
TITLE:	Total synthesis of epothilone E and analogs with modified side chains through the Stille coupling reaction
AUTHOR(S):	Nicolaou, K. C.; He, Yun; Roschangar, Frank; King, N. Paul; Vourloumis, Dionisios; Li, Tianhu
CORPORATE SOURCE:	Department of Chemistry, Skaggs Inst. for Chemical Biology, Scripps Res. Inst., La Jolla, CA, 92037, USA
SOURCE:	Angewandte Chemie, International Edition (1998), 37(1/2), 84-87
	CODEN: ACIEF5; ISSN: 1433-7851
PUBLISHER:	Wiley-VCH Verlag GmbH
DOCUMENT TYPE:	Journal
LANGUAGE:	English
OTHER SOURCE(S):	CASREACT 128:230166
GI	



AB The first total synthesis of epothilone E [I; R = 2-(hydroxymethyl)thiazol-4-yl, X = O] in which an olefin metathesis is used to form the macrocyclic lactone and a Stille coupling reaction is used to form the side chain is reported. The Stille coupling reaction was used to prep. deoxygenated side-chain analogs I [R = thiazol-4-yl, thiazol-5-yl, thiazol-2-yl, 2-(5-acetoxypentyl)thiazol-4-yl, 2-piperidinethiazol-4-yl, 2-(methylthio)thiazol-4-yl, 2-furyl, 2-thienyl, Ph, 3-pyridyl; X = bond].

IT **204513-12-2P**, Desoxyepothilone E

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

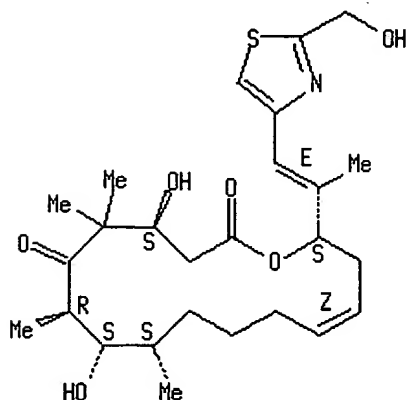
(total synthesis of epothilone E and analogs through the Stille coupling reaction)

RN **204513-12-2** HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-16-[(1E)-2-[2-(hydroxymethyl)-4-thiazolyl]-1-methylethenyl]-5,5,7,9-tetramethyl-, (4S,7R,8S,9S,13Z,16S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

Double bond geometry as shown.



L6 ANSWER 15 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER: 1998:121923 HCAPLUS

DOCUMENT NUMBER: 128:252599

TITLE: Farnesyl transferase inhibitors cause enhanced mitotic sensitivity to taxol and epothilones

AUTHOR(S): Moasser, Mark M.; Sepp-Lorenzino, Laura; Kohl, Nancy E.; Oliff, Allen; Balog, Aaron; Su, Dai-Shi; Danishefsky, Samuel J.; Rosen, Neal

CORPORATE SOURCE: Department of Medicine, Memorial Sloan-Kettering Cancer Center, Sloan-Kettering Institute, New York, NY, 10021, USA

SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1998), 95(4), 1369-1374
CODEN: PNASA6; ISSN: 0027-8424

PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB An important class of cellular proteins, which includes members of the p21ras family, undergoes post-translational farnesylation, a modification required for their partition to membranes. Specific farnesyl transferase inhibitors (FTIs) have been developed that selectively inhibit the processing of these proteins. FTIs have been shown to be potent inhibitors of tumor cell growth in cell culture and in murine models and at doses that cause little toxicity to the animal. These data suggest that these drugs might be useful therapeutic agents. We now report that, when FTI is combined with some cytotoxic antineoplastic drugs, the effects on tumor cells are additive. No interference is noted. Furthermore, FTI and agents that prevent microtubule depolymerization, such as taxol or epothilones, act synergistically to inhibit cell growth. FTI causes increased sensitivity to induction of metaphase block by these agents, suggesting that a farnesylated protein may regulate the mitotic check point. The findings imply that FTI may be a useful agent for the treatment of tumors with wild-type ras that are sensitive to taxanes.

IT **186692-73-9**, Desoxyepothilone A

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

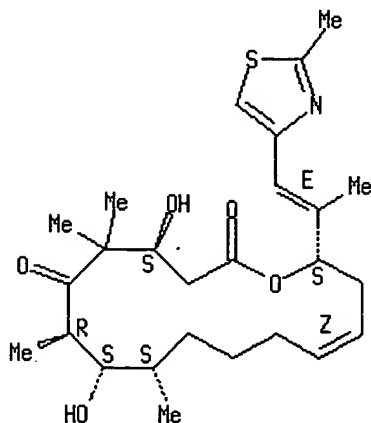
(farnesyl transferase inhibitors cause enhanced mitotic sensitivity to taxol and epothilones)

RN **186692-73-9** HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

Double bond geometry as shown.



L6 ANSWER 16 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER: 1998:50907 HCAPLUS

DOCUMENT NUMBER: 128:180246

TITLE: Total synthesis of oxazole- and cyclopropane-containing epothilone B analogs by the macrolactonization approach

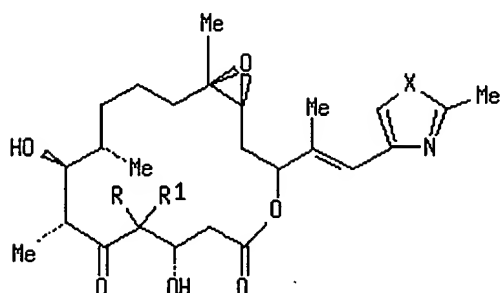
AUTHOR(S): Nicolaou, K. C.; Sarabia, Francisco; Finlay, M. Ray V.; Ninkovic, Sacha; King, N. Paul; Vourloumis, Dionisios; He, Yun

CORPORATE SOURCE: Department of Chemistry and The Skaggs Institute for Chemical Biology The Scripps Research Institute, La Jolla, CA, 92037, USA

SOURCE: Chemistry--A European Journal (1997), 3(12), 1971-1986

PUBLISHER:
DOCUMENT TYPE:
LANGUAGE:
GI

CODEN: CEUJED; ISSN: 0947-6539
Wiley-VCH Verlag GmbH
Journal
English



I

AB In order to probe structure-activity relationships in the epothilone area, two series of epothilone B analogs were designed and synthesized. The first series contg. an oxazole moiety in place of a thiazole on the side chain was constructed via utilization of key intermediates whereas the second series contg. an ethano group instead of the gem-di-Me group at position 4 was synthesized. A Yamaguchi-type macrolactonization reaction was used to construct the macrocycle from a secoacid, which was assembled, in both cases, via a) an aldol reaction, b) an Enders alkylation, and c) a Wittig-type reaction. This convergent strategy provided access to oxazole and 4,4-ethano analogs, e.g., I (R = R1 = Me, X = O, S; RR1 = CH2CH2, X = O, S).

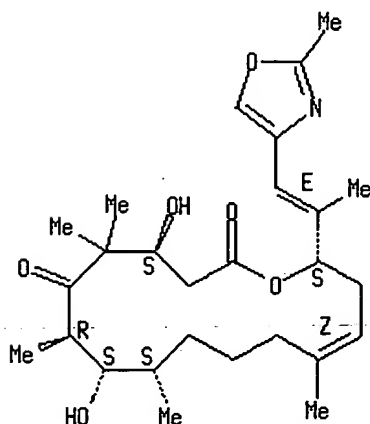
IT 198571-09-4P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(total synthesis of oxazole- and cyclopropane-contg. epothilone B analogs via macrolactonization)

RN 198571-09-4 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[(1E)-1-methyl-2-(2-methyl-4-oxazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L6 ANSWER 17 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text Citing
References

ACCESSION NUMBER: 1998:50906 HCAPLUS
DOCUMENT NUMBER: 128:140541

TITLE: Total synthesis of oxazole- and cyclopropane-containing epothilone A analogs by the olefin metathesis approach

AUTHOR(S): Nicolaou, K. C.; Vallberg, Hans; King, N. Paul; Roschangar, Frank; He, Yun; Vourloumis, Dionisios; Nicolaou, Christopher G.

CORPORATE SOURCE: Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, CA, 92037, USA

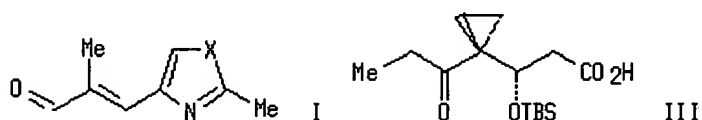
SOURCE: Chemistry--A European Journal (1997), 3(12), 1957-1970
CODEN: CEUJED; ISSN: 0947-6539

PUBLISHER: Wiley-VCH Verlag GmbH

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



AB For structure-activity relationship studies, two series of epothilone A analogs have been designed and synthesized, one contg. an oxazole moiety instead of the thiazole heterocycle and the other contg. a spirocyclopropane moiety in place of the gem-di-Me group at position C-4 (4,4-ethano-epothilones). The olefin metathesis strategy in soln. was utilized for the chem. synthesis of these compds. starting with key building blocks (I) (X = O), (S)-H₂C=CH(CH₂)₃CH(Me)CHO (II), (S)-MeCH₂COCMe₂CH(OSiMe₂CMe₃)CH₂CO₂H for the oxazole series and building blocks I (X = S), II, and (III) for the 4,4-ethano series. The convergent strategy towards the designed epothilone A series involved: a- an aldol condensation reaction, b- an esterification reaction, c- an olefin metathesis reaction catalyzed by [RuCl₂(=CHPh)-(PCy₃)₂], and d- epoxidn. of the macrocycle double bond.

IT 198475-12-6P

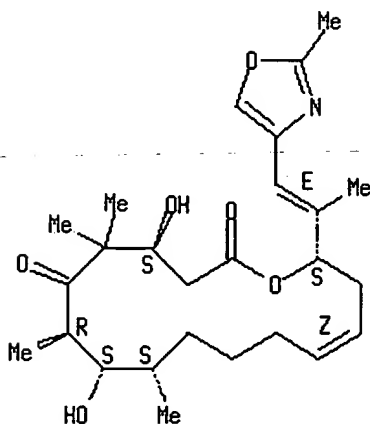
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(total synthesis of oxazole- and cyclopropane-contg. epothilone A analogs by the olefin metathesis approach)

RN 198475-12-6 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-oxazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.

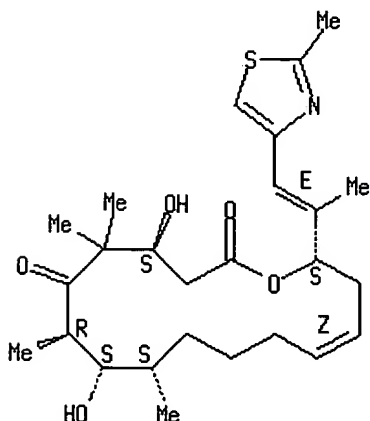


L6 ANSWER 18 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER: 1998:729 HCAPLUS
 DOCUMENT NUMBER: 128:88685
 TITLE: Metathesis vs metastasis: the chemistry and biology of the epothilones
 AUTHOR(S): Finlay, Ray
 CORPORATE SOURCE: Dep. Chemistry, The Skaggs Inst. for Chemical Biol., The Scripps Res. Inst., La Jolla, CA, 92037, USA
 SOURCE: Chemistry & Industry (London) (1997), (24), 991-996
 CODEN: CHINAG; ISSN: 0009-3068
 PUBLISHER: Society of Chemical Industry
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: English
 AB A review with 15 refs. on a recent entry onto the scene of potentially useful natural products, the epothilones A - E, providing valuable information for the fight against cancer via their interaction with microtubules.
 IT **186692-73-9P**, Epothilone C
 RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); USES (Uses)
 (chem. and bioactivity of the epothilones)
 RN **186692-73-9** HCAPLUS
 CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
 Double bond geometry as shown.

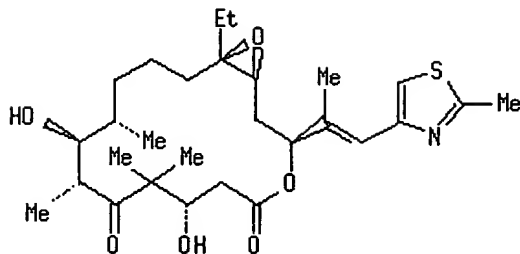


L6 ANSWER 19 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER: 1997:787450 HCAPLUS
 DOCUMENT NUMBER: 128:101936
 TITLE: Total synthesis of 26-hydroxyepothilone B and related analogs
 AUTHOR(S): Nicolaou, K. C.; Ninkovic, Sacha; Finlay, M. Ray V.; Sarabia, Francisco; Li, Tianhu
 CORPORATE SOURCE: Department of Chemistry and Biochemistry, University of California, California, 92093, USA
 SOURCE: Chemical Communications (Cambridge) (1997), (24), 2343-2344

PUBLISHER: CODEN: CHCOFS; ISSN: 1359-7345
 DOCUMENT TYPE: Royal Society of Chemistry
 LANGUAGE: Journal
 OTHER SOURCE(S): English
 GI CASREACT 128:101936



AB A series of 26-substituted epothilones B, e.g. I, were constructed by total synthesis involving a selective Wittig olefination, an aldol reaction and a macrolactonization as key steps.

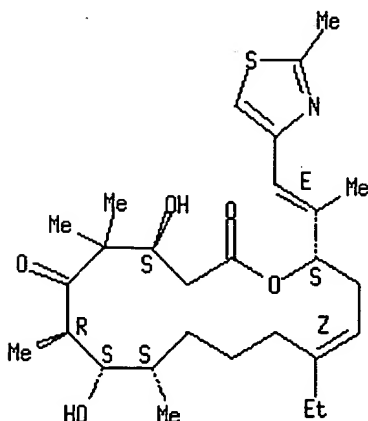
IT 198475-04-6P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
 (total synthesis of 26-hydroxyepothilone B and related analogs)

RN 198475-04-6 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 13-ethyl-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
 Double bond geometry as shown.



L6 ANSWER 20 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER:	1997:724919 HCAPLUS
DOCUMENT NUMBER:	127:346221
TITLE:	Synthesis of epothilones A and B in solid and solution phase. [Erratum to document cited in CA127:4950]
AUTHOR(S):	Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Ninkovic, S.; Sarabia, F.; He, Y.; Vourloumis, D.; Yang, Z.; Li, T.; Giannakakou, P.; Hamel, E.
CORPORATE SOURCE:	Dep. Chemistry, Skaggs Inst. Chem. Biology, Scripps Res. Inst., La Jolla, CA, 92037, USA
SOURCE:	Nature (London) (1997), 390(6655), 100

CODEN: NATUAS; ISSN: 0028-0836
 PUBLISHER: Macmillan Magazines
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Ref. 19, includes, in addn. to a total synthesis of epothilone B, biol. data for compd. 23 and other congeners similar to the reported in the Letter.

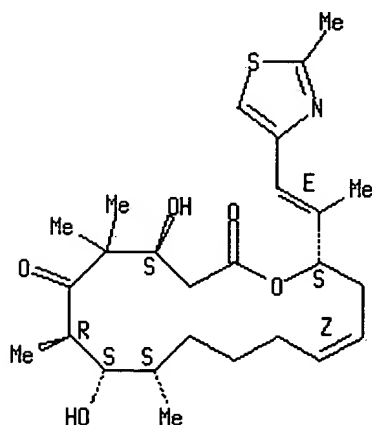
IT 186692-73-9P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
 (prepn. of a combinatorial library via solid-phase synthesis of epothilone A and soln.-phase synthesis of epothilone B (Erratum))

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
 Double bond geometry as shown.



L6 ANSWER 21 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER: 1997:714315 HCAPLUS
 DOCUMENT NUMBER: 128:3560
 TITLE: Designed epothilones: combinatorial synthesis, tubulin assembly properties, and cytotoxic action against taxol-resistant tumor cells
 AUTHOR(S): Nicolaou, K. C.; Vourloumis, Dionisios; Li, Tianhu; Pastor, Joaquin; Winssinger, Nicolas; He, Yun; Ninkovic, Sacha; Sarabia, Francisco; Vallberg, Hans; Roschangar, Frank; King, N. Paul; Finlay, M. Ray V.; Giannakakou, Pareskevi; Verdier-Pinard, Pascal; Hamel, Ernest
 CORPORATE SOURCE: Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, CA, 92037, USA
 SOURCE: Angewandte Chemie, International Edition in English (1997), 36(19), 2097-2103
 CODEN: ACIEAY; ISSN: 0570-0833
 PUBLISHER: Wiley-VCH
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB The title work demonstrates the power of interfacing combinatorial chem. with chem. biol. as facilitated by solid-phase synthesis, radiofrequency encoded combinatorial chem. and modern biol. assays. A library of 112 epothilones were prepd. by solid-phase synthesis, their structure activity

relationships measured by tubulin binding assay and some tested for inhibition of carcinoma cell growth.

IT **186692-73-9P**

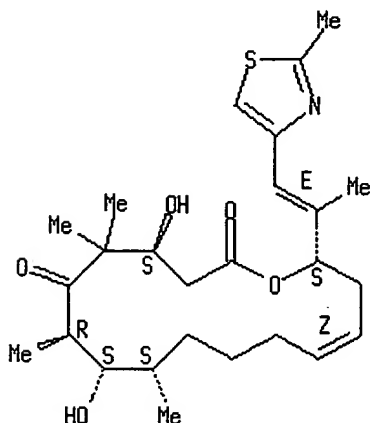
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(combinatorial synthesis of epothilone library, tubulin assembly properties, and cytotoxic action against taxol-resistant tumor cells)

RN **186692-73-9** HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

Double bond geometry as shown.



L6 ANSWER 22 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER: 1997:714314 HCAPLUS

DOCUMENT NUMBER: 127:358730

TITLE: Structure-activity relationships of the epothilones and the first in vivo comparison with paclitaxel

AUTHOR(S): Su, Dai-Shi; Balog, Aaron; Meng, Dongfang; Bertinato, Peter; Danishefsky, Samuel J.; Zheng, Yu-Huang; Chou, Ting-Chao; He, Lifeng; Horwitz, Susan B.

CORPORATE SOURCE: Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, New York, NY, 10021, USA

SOURCE: Angewandte Chemie, International Edition in English (1997), 36(19), 2093-2096

CODEN: ACIEAY; ISSN: 0570-0833

PUBLISHER: Wiley-VCH

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The structure-activity relationships of the epothilones and 18 derivs. and analogs were studied. An in vivo comparison of the chemotherapeutic effect of epothilone B with that of paclitaxel was also studied. The chemotherapeutic effect of daily doses of epothilone B (0.7 mg/kg) and paclitaxel (2 mg/kg) in CB-17 SCID mice bearing drug-resistant human CCRF-CEM/VBL xenografts were T/C = 0.33 and T/C = 0.70, resp.

IT **186692-73-9**, Desoxyepothilone A

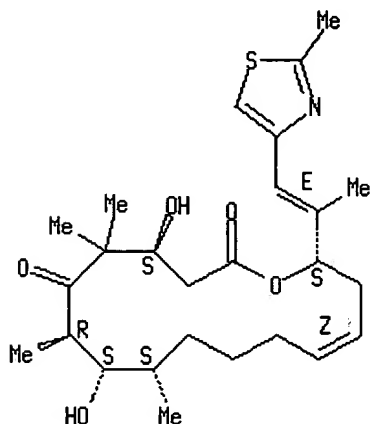
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(structure-activity relationships of the epothilones and in vivo comparison with paclitaxel)

RN **186692-73-9** HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-

[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-
(9CI) (CA INDEX NAME)

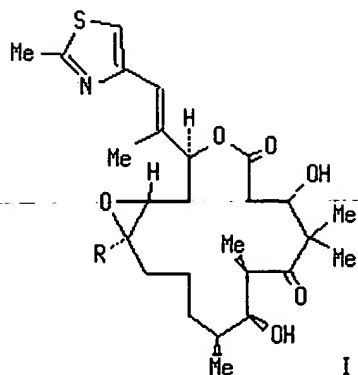
Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L6 ANSWER 23 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER:	1997:665094 HCAPLUS
DOCUMENT NUMBER:	127:293040
TITLE:	Total Syntheses of Epothilones A and B
AUTHOR(S):	Meng, Dongfang; Bertinato, Peter; Balog, Aaron; Su, Dai-Shi; Kamenecka, Ted; Sorensen, Erik; Danishefsky, Samuel J.
CORPORATE SOURCE:	Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, New York, NY, 10021, USA
SOURCE:	Journal of the American Chemical Society (1997), 119(42), 10073-10092 CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER:	American Chemical Society
DOCUMENT TYPE:	Journal
LANGUAGE:	English
OTHER SOURCE(S):	CASREACT 127:293040
GI	



AB Convergent, stereocontrolled total syntheses of the microtubule-stabilizing macrolides epothilones A (I; R = H) and B (I; R = Me) have

been achieved. Four distinct ring-forming strategies were pursued. Of these four, three were reduced to practice. In one approach, the action of a base on a substance possessing an acetate ester and a nonenolizable aldehyde brought about a remarkably effective macroaldolization simultaneously creating the C2-C3 bond and the hydroxyl-bearing stereocenter at C-3. Alternatively, the 16-membered macrolide of the epothilones could be fashioned through a C12-C13 ring-closing olefin metathesis and through macrolactonization of the appropriate hydroxy acid. The application of a stereospecific B-alkyl Suzuki coupling strategy permitted the establishment of a cis C12-C13 olefin, thus setting the stage for an eventual site- and diastereoselective epoxidn. reaction. The development of a novel cyclopropane solvolysis strategy for incorporating the geminal Me groups of the epothilones, and the use of Lewis acid catalyzed diene-aldehyde cyclocondensation (LACDAC) and asym. allylation methodol. are also noteworthy.

IT **186692-73-9P**, (-)-Desoxyepothilone A

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

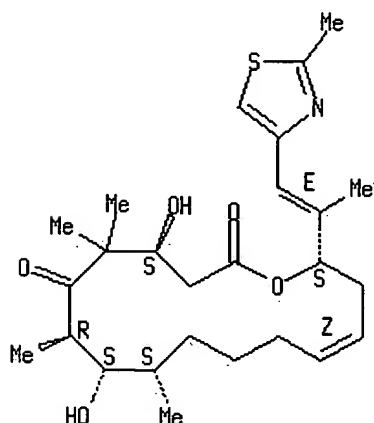
(syntheses of epothilones A and B via macroaldolization, olefin metathesis and macrolactonization)

RN **186692-73-9** HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

Double bond geometry as shown.



L6 ANSWER 24 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER: 1997:528753 HCAPLUS

DOCUMENT NUMBER: 127:135660

TITLE: Total Syntheses of Epothilones A and B via a Macrolactonization-Based Strategy

AUTHOR(S): Nicolaou, K. C.; Ninkovic, S.; Sarabia, F.; Vourloumis, D.; He, Y.; Vallberg, H.; Finlay, M. R. V.; Yang, Z.

CORPORATE SOURCE: Department of Chemistry and The Skaggs, Institute for Chemical Biology, La Jolla, CA, 92037, USA

SOURCE: Journal of the American Chemical Society (1997), 119(34), 7974-7991

CODEN: JACSAT; ISSN: 0002-7863

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 127:135660

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The total syntheses of epothilones A (I) (R = H) and B I (R = Me) and several analogs are described. The reported strategy relies on a macrolactonization approach and features selective epoxidn. of the macrocycle double bond in precursors II (R = H, Me) as well as high convergency and flexibility. Building blocks (S)-MeCH₂COC(Me)CH(OSiMe₂CM₃)CH₂CO₂H, (S)-Me₃CM₂SiOCH₂CH(Me)CH₂CH₂CH₂COR (R = H, Me), (III) [R₂ = CH₂CH₂P+(Ph)₃I⁻; CH₂CHO] were constructed by asym. processes and coupled via Wittig, aldol, and macrolactonization reactions to afford the basic skeleton of epothilones and that of several of their analogs by a relatively short route. The utilization of intermediate III [R₂ = (E)-CH₂CH=C(Me)CH₂CH₂CH₂I], obtained via a stereoselective Wittig reaction and its Enders coupling to SAMP hydrazone, in combination with a stereoselective aldol reaction with the modified substrate (S)-MeCH₂COC(Me)CH(OSiMe₂CM₃)CH₂CH₂OSiMe₂CM₃ improved the stereoselectivity and efficiency of the total synthesis of these new and highly potent microtubule binding antitumor agents.

IT **186692-73-9P**

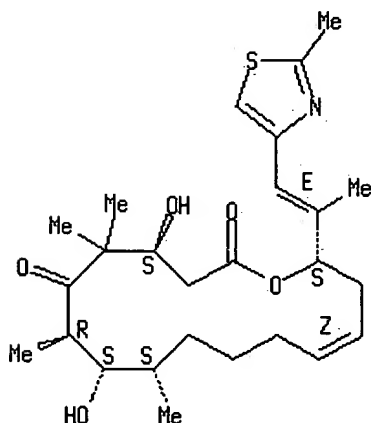
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(total syntheses of epothilones A and B via a macrolactonization-based strategy)

RN **186692-73-9** HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L6 ANSWER 25 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER:	1997:528752 HCAPLUS
DOCUMENT NUMBER:	127:149021
TITLE:	The Olefin Metathesis Approach to Epothilone A and Its Analogs
AUTHOR(S):	Nicolaou, K. C.; He, Y.; Vourloumis, D.; Vallberg, H.; Roschangar, F.; Sarabia, F.; S.Ninkovic; Yang, Z.; Trujillo, J. I.
CORPORATE SOURCE:	Department of Chemistry and The Skaggs, Institute for Chemical Biology, La Jolla, CA, 92037, USA
SOURCE:	Journal of the American Chemical Society (1997),

119(34), 7960-7973
CODEN: JACSAT; ISSN: 0002-7863
American Chemical Society

PUBLISHER:
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 127:149021

GI For diagram(s), see printed CA Issue.

AB The olefin metathesis approach to epothilone A (I) and several diastereomeric analogs is described. Key building blocks II, (S)-OHCH(Me)CH₂CH₂CH=CH₂, and (S)-MeCH₂COC(Me)₂CH(OSiMe₂CMe₃)CH₂CO₂H were constructed in optically active form and were coupled and elaborated to olefin metathesis precursor III (R = SiMe₂CMe₃) via an aldol reaction and an esterification coupling. Olefin metathesis of compd. III (R = SiMe₂CMe₃), under the catalytic influence of RuCl₂(:CHPh)(PCy₃)₂, furnished cis- and trans-cyclic olefins IV (R = SiMe₂CMe₃). Epoxidn. of (Z)-IV (R = H) gave I and several analogs, whereas epoxidn. of (E)-IV (R = H) resulted in addnl. epothilones. Similar elaboration of isomeric as well as simpler intermediates resulted in yet another series of epothilone analogs and model systems.

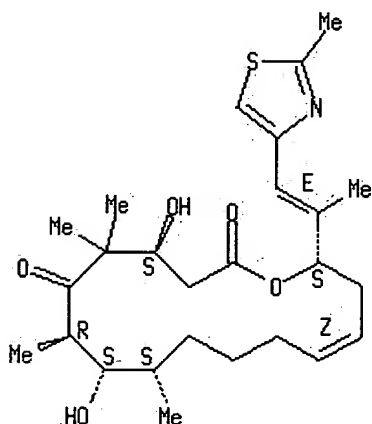
IT **186692-73-9P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of epothilone A and analogs via olefin metathesis)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L6 ANSWER 26 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text Citing
References

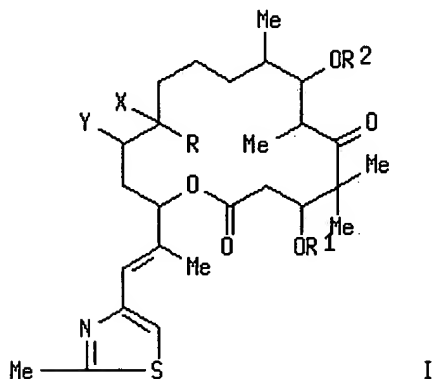
ACCESSION NUMBER: 1997:456769 HCAPLUS
DOCUMENT NUMBER: 127:50474
TITLE: Preparation of epothilone derivatives as agrochemicals and pharmaceuticals

INVENTOR(S): Hoefle, Gerhard; Kiffe, Michael
PATENT ASSIGNEE(S): Gesellschaft fuer Biotechnologische Forschung MbH (Gbf), Germany
SOURCE: Ger. Offen., 9 pp.
CODEN: GWXXBX

DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19542986	A1	19970522	DE 1995-19542986	19951117
WO 9719086	A1	19970529	WO 1996-EP5080	19961118
W: JP, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 873341	A1	19981028	EP 1996-939097	19961118
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
EP 903348	A1	19990324	EP 1998-121523	19961118
EP 903348	B1	20020605		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2000500757	T2	20000125	JP 1997-519381	19961118
EP 1186606	A1	20020313	EP 2001-127352	19961118
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
AT 218556	E	20020615	AT 1998-121523	19961118
US 6288237	B1	20010911	US 1998-77055	19980803
US 2001034452	A1	20011025	US 2001-836134	20010416
PRIORITY APPLN. INFO.:				
			DE 1995-19542986	A 19951117
			DE 1996-19639456	A 19960925
			EP 1996-939097	A3 19961118
			WO 1996-EP5080	W 19961118
			US 1998-77055	A3 19980803

OTHER SOURCE(S): MARPAT 127:50474
GI



AB The title compds., e.g., I [R = H, C1-4 alkyl; R1, R2 = H, C1-6 alkyl, C1-6 acyl, benzoyl, C1-4 trialkylsilyl, benzyl, Ph, C1-6 alkoxy, C6 alkyl-, hydroxy-, and halo-substituted benzyl or phenyl; X, Y = halo, OH, acyloxy, alkoxy, benzoyloxy], useful as agrochems. and pharmaceuticals (no data), are prepd. Thus, epothilone A in acetone contg. trifluoroacetic acid was heated overnight at 50° and the reaction mixt. was adjusted to pH 7 with 1 M phosphate buffer to give 2 isomers, each in 19% yield.

IT 191105-82-5P

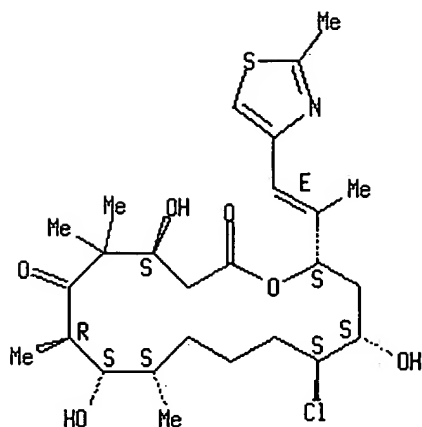
RL: AGR (Agricultural use); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(prepn. of epothilone derivs. as agrochems. and pharmaceuticals)

RN 191105-82-5 HCAPLUS

CN Oxacyclohexadecane-2,6-dione, 13-chloro-4,8,14-trihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, [4R*,7S*,8R*,9R*,13R*,14R*,16R*(E)]- (9CI) (CA INDEX NAME)

Relative stereochemistry.
Double bond geometry as shown.

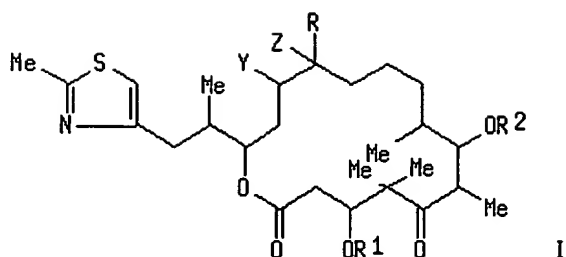


L6 ANSWER 27 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER: 1997:443365 HCAPLUS
 DOCUMENT NUMBER: 127:81289
 TITLE: Preparation of epothilone derivatives as agrochemicals and pharmaceuticals
 INVENTOR(S): Hofle, Gerhard; Kiffe, Michael
 PATENT ASSIGNEE(S): Gesellschaft Fur Biotechnologische Forschung Mbh (Gbf), Germany; Hofle, Gerhard; Kiffe, Michael
 SOURCE: PCT Int. Appl., 38 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: German
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
<u>WO 9719086</u>	A1	19970529	<u>WO 1996-EP5080</u>	19961118
W: JP, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
<u>DE 19542986</u>	A1	19970522	<u>DE 1995-19542986</u>	19951117
<u>DE 19639456</u>	A1	19980326	<u>DE 1996-19639456</u>	19960925
<u>EP 873341</u>	A1	19981028	<u>EP 1996-939097</u>	19961118
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
<u>JP 2000500757</u>	T2	20000125	<u>JP 1997-519381</u>	19961118
<u>US 6288237</u>	B1	20010911	<u>US 1998-77055</u>	19980803
PRIORITY APPLN. INFO.:			<u>DE 1995-19542986</u>	A 19951117
			<u>DE 1996-19639456</u>	A 19960925
			<u>WO 1996-EP5080</u>	W 19961118
OTHER SOURCE(S):		MARPAT 127:81289		
GI				



AB The title compds., e.g., I [R = H, C1-4 alkyl; R1, R2 = H, C1-6 alkyl, C1-6 acyl, benzoyl, C1-4 trialkylsilyl, benzyl, Ph, C1-6 alkoxy, C6 alkyl-, hydroxy-, and halo-substituted benzyl or phenyl; X, Y = H, halo, pseudohalo, OH, acyloxy, alkoxy, benzoyloxy; or YZ = O, bond; however, I may not be epothilone A or B], useful as agrochems. and pharmaceuticals (no data), are prepd. Thus, epothilone A in acetone contg. trifluoroacetic acid was heated overnight at 50° and the reaction mixt. was adjusted to pH 7 with 1 M phosphate buffer to give 2 isomers, each in 19% yield.

IT **191105-82-5P**

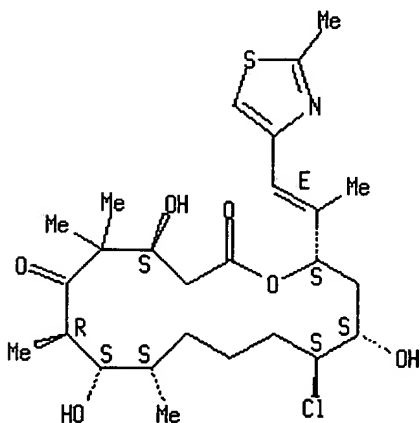
RL: AGR (Agricultural use); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(prepn. of epothilone derivs. as agrochems. and pharmaceuticals)

RN **191105-82-5** HCAPLUS

CN Oxacyclohexadecane-2,6-dione, 13-chloro-4,8,14-trihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, [4R*,7S*,8R*,9R*,13R*,14R*,16R*(E)]- (9CI) (CA INDEX NAME)

Relative stereochemistry.
Double bond geometry as shown.

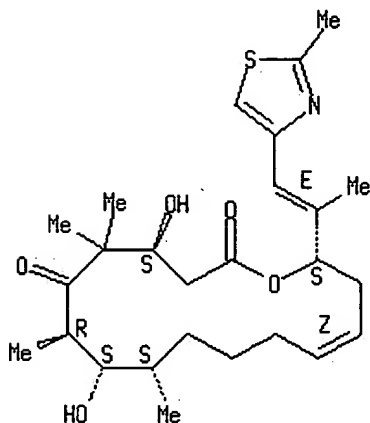


L6 ANSWER 28 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
ACCESSION NUMBER:	1997:430309 HCAPLUS
DOCUMENT NUMBER:	127:108793
TITLE:	Stereoselective syntheses and evaluation of compounds in the 8-desmethylepothilone A series: some surprising observations regarding their chemical and biological properties
AUTHOR(S):	Balog, Aaron; Betinato, Peter; Su, Dai-Shi; Meng, Dongfang; Sorensen, Erik; Danishefsky, Samuel J.; Zheng, Yu-Huang; Chou, Ting-Chao; He, Lifeng; Horwitz, Susan B.
CORPORATE SOURCE:	Lab. Bioorganic Chem., Sloan-Kettering Inst. Cancer Res., New York, NY, 10021, USA

SOURCE: Tetrahedron Letters (1997), 38(26), 4529-4532
 CODEN: TELEAY; ISSN: 0040-4039
 PUBLISHER: Elsevier
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 OTHER SOURCE(S): CASREACT 127:108793
 AB The title compds. have been synthesized in a convergent way by recourse to a Weiler type dianion construction.
 IT **186692-73-9**, Desoxyepothilone A
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
 (stereoselective syntheses and evaluation of compds. in the 8-desmethylepothilone A series)
 RN **186692-73-9** HCAPLUS
 CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

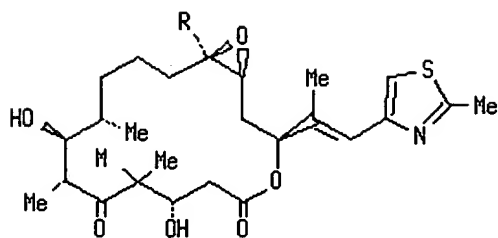
Absolute stereochemistry. Rotation (-).
 Double bond geometry as shown.



L6 ANSWER 29 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER:	1997:330310 HCAPLUS
DOCUMENT NUMBER:	127:4950
TITLE:	Synthesis of epothilones A and B in solid and solution phase
AUTHOR(S):	Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Ninkovic, S.; Sarabia, F.; He, Y.; Vourloumis, D.; Yang, Z.; Li, T.; Giannakakou, P.; Hamel, E.
CORPORATE SOURCE:	Dep. Chemistry, Skaggs Inst. Chem. Biology, Scripps Res. Inst., La Jolla, CA, 92037, USA
SOURCE:	Nature (London) (1997), 387(6630), 268-272 CODEN: NATUAS; ISSN: 0028-0836
PUBLISHER:	Macmillan Magazines
DOCUMENT TYPE:	Journal
LANGUAGE:	English
OTHER SOURCE(S):	CASREACT 127:4950
GI	



I

AB Epothilones A (I; R = H) and B (I: R = Me), two compds. that were recently isolated from myxobacterium *Sorangium cellulosum* strain 90, have generated intense interest among chemists, biologists and clinicians owing to the structural complexity, unusual mechanism of interaction with microtubules and anticancer potential of these mols. Like taxol, they exhibit cytotoxicity against tumor cells by inducing microtubule assembly and stabilization, even in taxol-resistant cell lines. Following the structural elucidation of these mols. by X-ray crystallog. in 1996, several synthesis of epothilones A and B have been reported, indicative of the potential importance of these mols. in the cancer field. Here we report the first solid-phase synthesis of epothilone A, the total synthesis of epothilone B, and the generation of a small epothilone library. The solid-phase synthesis applied here to epothilone A could open up new possibilities in natural-product synthesis and, together with soln.-phase synthesis of other epothilones, paves the way for the generation of large combinatorial libraries of these important mols. for biol. screening.

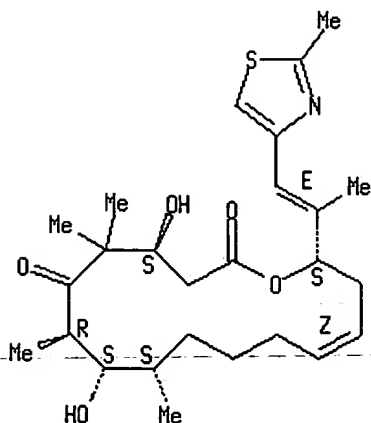
IT 186692-73-9P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent) (prepn. of a combinatorial library via solid-phase synthesis of epothilone A and soln.-phase synthesis of epothilone B)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L6 ANSWER 30 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full
Text

Citing
References

ACCESSION NUMBER:

1997:302059 HCAPLUS

DOCUMENT NUMBER:

127:4948

TITLE:

Total synthesis of (-)-epothilone B: an extension of

the Suzuki coupling method and insights into structure-activity relationships of the epothilones

AUTHOR(S): Su, Dai-Shi; Meng, Dongfang; Bertinato, Peter; Balog, Aaron; Sorensen, Erik J.; Danishefsky, Samuel J.; Zheng, Yu-Huang; Chou, Ting-Chao; He, Lifeng; Horwitz, Susan B.

CORPORATE SOURCE: Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, New York, NY, 10021, USA

SOURCE: Angewandte Chemie, International Edition in English (1997), 36(7), 757-759
CODEN: ACIEAY; ISSN: 0570-0833

PUBLISHER: VCH

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 127:4948

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB (-)-Epothilone B (I; R = Me, X = O) and desoxyepothilone B (I; R = Me, X = bond) were prepd. via Suzuki coupling of (Z)-vinyl iodide II with borane III. I (R = H, Me, X = O, bond) and the E-isomers of I (R = H, Me, X = bond) were tested for efficacy against drug-sensitive and resistant CCRF-CEM cell lines (IC₅₀ = 0.0004 - 0.262 μM).

IT **186692-73-9**, Desoxyepothilone A

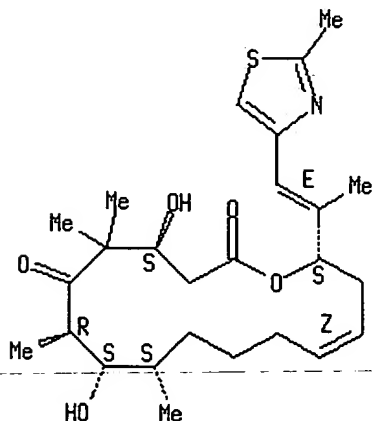
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(synthesis of epothilone B via a Suzuki coupling and insights into antitumor structure-activity relationships)

RN **186692-73-9** HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.

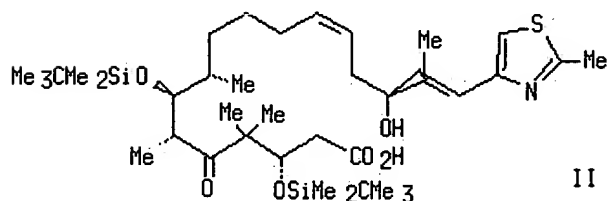
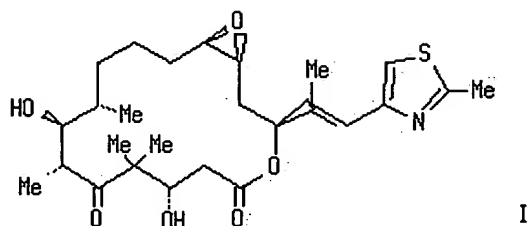


L6 ANSWER 31 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER: 1997:206419 HCAPLUS
DOCUMENT NUMBER: 126:251010
TITLE: Total synthesis of epothilone A: the

macrolactonization approach
 AUTHOR(S): Nicolaou, K. C.; Sarabia, Francisco; Ninkovic, Sacha; Yang, Zhen
 CORPORATE SOURCE: Dep. Chem., Skaggs Inst. Chem. Biol. Scripps Res. Inst., La Jolla, CA, 92037, USA
 SOURCE: Angewandte Chemie, International Edition in English (1997), 36(5), 525-527
 CODEN: ACIEAY; ISSN: 0570-0833
 PUBLISHER: VCH
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 OTHER SOURCE(S): CASREACT 126:251010
 GI



AB Epothilone A (I) was prepd. via a highly convergent and flexible route with macrolactonization of hydroxy acid II as the key step.

IT **186692-73-9P**

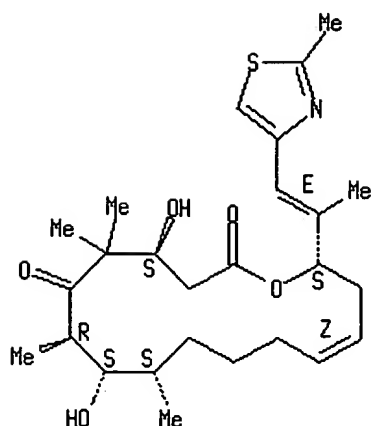
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(total synthesis of epothilone A via a macrolactonization approach)

RN **186692-73-9** HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

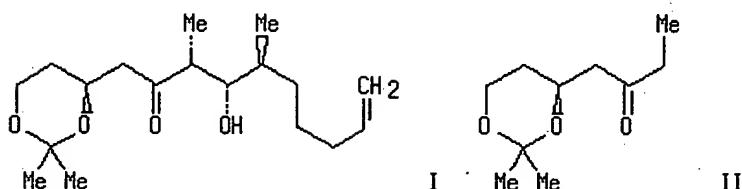
Absolute stereochemistry. Rotation (-).
 Double bond geometry as shown.



L6 ANSWER 32 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER: 1997:206418 HCAPLUS
 DOCUMENT NUMBER: 126:277316
 TITLE: Total synthesis of (-)-epothilone A
 AUTHOR(S): Schinzer, Dieter; Limberg, Anja; Bauer, Armin; Boehm, Oliver M.; Cordes, Martin
 CORPORATE SOURCE: Dip. Chim., Inst. Org. Chem. Tech. Univ. Hagenring, Braunschweig, D-38106, Germany
 SOURCE: Angewandte Chemie, International Edition in English (1997), 36(5), 523-524
 CODEN: ACIEAY; ISSN: 0570-0833
 PUBLISHER: VCH
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 OTHER SOURCE(S): CASREACT 126:277316
 GI



AB Stereoselective total synthesis of (-)-epothilone A and epothilone C was reported. The key step was the diastereoselective prepn. of intermediate ketone I by an aldol condensation of II with (S)-2-methyl-6-heptenal.

IT 186692-73-9P, Epothilone C

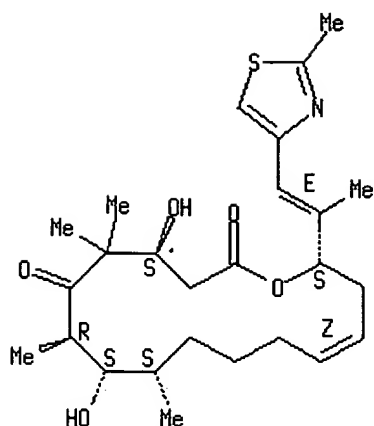
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(total synthesis of (-)-epothilone A)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
 Double bond geometry as shown.



L6 ANSWER 33 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER: 1997:175662 HCAPLUS
 DOCUMENT NUMBER: 126:225133
 TITLE: Remote Effects in Macrolide Formation through Ring-Forming Olefin Metathesis: An Application to the Synthesis of Fully Active Epothilone Congeners
 AUTHOR(S): Meng, Dongfang; Su, Dai-Shi; Balog, Aaron; Bertinato, Peter; Sorensen, Erik J.; Danishefsky, Samuel J.; Zheng, Yu-Huang; Chou, Ting-Chao; He, Lifeng; Horwitz, Susan B.
 CORPORATE SOURCE: Laboratories for Bioorganic Chemistry and Biochemical Pharmacology, Sloan-Kettering Institute for Cancer Research, New York, NY, 10021, USA
 SOURCE: Journal of the American Chemical Society (1997), 119(11), 2733-2734
 CODEN: JACSAT; ISSN: 0002-7863
 PUBLISHER: American Chemical Society
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 OTHER SOURCE(S): CASREACT 126:225133
 GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

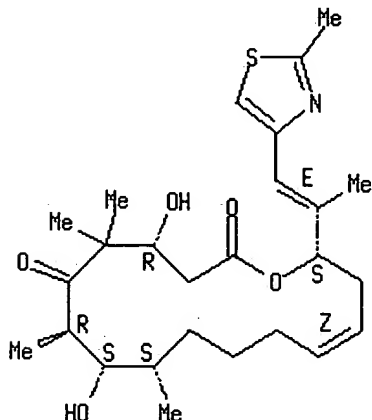
AB A ring closing olefin metathesis strategy for the synthesis of the previously encountered desoxyepothilone A (I) is described. A merging of the alkyl segment II (carbons 12-21) and acyl segment III (carbons 3-11) through an intermol. aldol-condensation reaction provided substrates needed for ring closing olefin metathesis. Thus, thiazole IV underwent olefin metathesis in C₆H₆ contg. 50 mol % (PhCH:)[P(cyclohexyl)₃]₂RuCl₂ to give 65% II and its E-isomer (Z:E 1:2). The results of these cyclization indicate a remarkable sensitivity to permutations of functionality at centers remote from the site of olefin metathesis. The in vitro biol. activity of E and Z desoxyepothilone as well as several related congeners is also described. I has IC₅₀ range of 0.012-0.022 μM against drug-sensitive and -resistant human leukemic CCRF-CEM cell lines.

IT 188259-95-2P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent) (prepn. of antitumor epothilone congeners via ring-forming olefin metathesis)

RN 188259-95-2 HCAPLUS
 CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-
 [(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4R,7R,8S,9S,13Z,16S)-
 (9CI) (CA INDEX NAME)

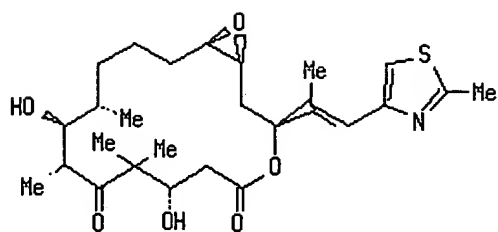
Absolute stereochemistry. Rotation (-).
 Double bond geometry as shown.



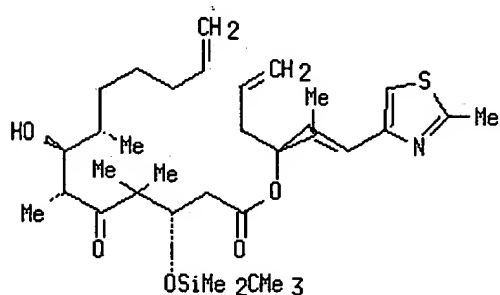
L6 ANSWER 34 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER:	1997:117381 HCAPLUS
DOCUMENT NUMBER:	126:199371
TITLE:	Total synthesis of epothilone A: the olefin metathesis approach
AUTHOR(S):	Yang, Zhen; He, Yun; Vourloumis, Dionisios; Vallberg, Hans; Nicolaou, K. C.
CORPORATE SOURCE:	Department Chemistry Skaggs Institute Chemical Biology, Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE:	Angewandte Chemie, International Edition in English (1997), 36(1/2), 166-168 CODEN: ACIEAY; ISSN: 0570-0833
PUBLISHER:	VCH
DOCUMENT TYPE:	Journal
LANGUAGE:	English
OTHER SOURCE(S):	CASREACT 126:199371
GI	



I



II

AB The asym. total synthesis of epothilone A (I) from EtCOCMe₂CHO, (S)-H₂C:CH(CH₂)₃CHMeCHO and Et 2-methylthiazole-4-carboxylate via metathesis of olefin II is described.

IT **186692-73-9P**

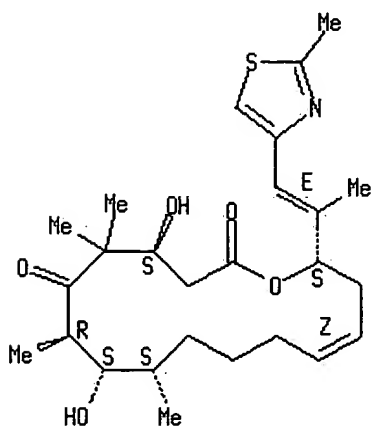
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(total synthesis of epothilone A via an olefin metathesis)

RN **186692-73-9** HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L6 ANSWER 35 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text	Citing References
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ACCESSION NUMBER:

1997:72321 HCAPLUS

DOCUMENT NUMBER:

126:144023

TITLE:

Total synthesis of (-)-epothilone A

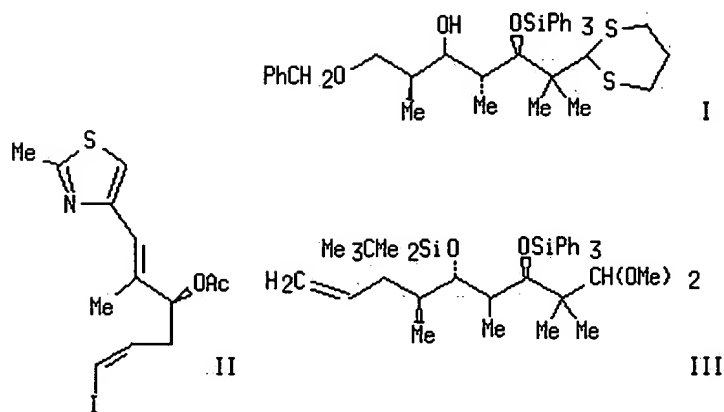
AUTHOR(S):

Balog, Aaron; Meng, Dongfang; Kamenecka, Ted; Bertinato, Peter; Su, Dai-Shi; Sorensen, Erik J.; Danishefsky, Samuel J.

CORPORATE SOURCE:

Lab. for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, New York, NY, 10021,

SOURCE: USA
 Angewandte Chemie, International Edition in English
 (1997), Volume Date 1996, 35(23/24), 2801-2803
 CODEN: ACIEAY; ISSN: 0570-0833
 PUBLISHER: VCH
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 GI



AB (-)-Epothilone A was prepd. from dithiane I, (R)-glycidol and [(2-methyl-1,3-thiazol-4-yl)methyl]diphenylphosphine oxide via a B-alkyl Suzuki coupling of thiazole II with acetal III followed by closure of the macrocycle with an aldol reaction.

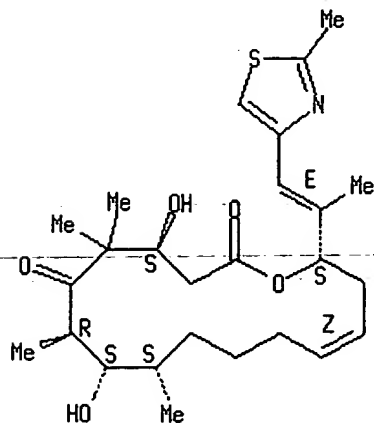
IT **186692-73-9P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
 (total synthesis of (-)-epothilone A via a B-alkyl Suzuki coupling followed by closure of the macrocycle with an aldol reaction)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
 Double bond geometry as shown.



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